Association of sedentary time and physical activity with insulin resistance among middle-aged Koreans: Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) study

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GLOSSARY OF TERMS

SB: Sedentary time

PA: Physical activity

MPA: Moderate-intensity physical activity

VPA: Vigorous-intensity physical activity

MVPA: Moderate to vigorous-intensity physical activity

BMI: Body mass index

FFQ : Food frequency questionnaire

HOMA-IR : Homeostasis model assessment of insulin resistance

CMERC cohort study: Cardiovascular and Metabolic Diseases Etiology Research Center cohort study

ABSTRACT

Association of sedentary time and physical activity with insulin resistance among middle-aged Koreans: Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) study

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Background:

The combined associations between sedentary time (SB) and physical activity (PA) with insulin resistance is poorly understood. The aim of this study is to examine the combined associations of sedentary time and physical activity with insulin resistance in middle-aged Korean adults.

Methods:

This cross-sectional study included 7,640 participants (2,575 men and 5,065 women) aged 30 to 64 years from the Cardiovascular and Metabolic Diseases Etiology Research Center study baseline enrollment (December 2013 to February 2018). Both sedentary time and physical activity measured by using a Korean version of the international physical activity questionnaire-short form (IPAQ-SF) were categorized into tertiles; (<28, 28-<49, or ≥49 h/wk for sedentary time) and (<9.9, 9.9-<30.6, or ≥30.6 metabolic equivalents (METs)-h/wk for physical activity). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated for the index of insulin resistance. Multivariate linear regression analysis was performed to assess the association between sedentary time/physical activity and HOMA-IR. And adjusted odds ratio (OR) and 95% confidence intervals (CIs) from a multivariate logistic regression model were generated to estimate the associations between sedentary time and physical activity with insulin resistance (HOMA-IR >1.6).

Results:

The statistically significant positive association between sedentary time as continuous variable with HOMA-IR [β (standard error; SE), p-value; 0.002 (0.000), <.0001], and negative association between physical activity as continuous

variable with HOMA-IR [β (SE), p-value; -0.002 (0.000), <.0001] were observed after fully adjustment. The associations of categories combined with sedentary time and physical activity with HOMA-IR were positive [p for trend; <.0001]. In the categories with sedentary time ≥49 h/wk and physical activity <9.9 METs-h/wk, the odds ratio for insulin resistance was 2.20 [95% CI; 1.75-2.77] compared to the reference group (sedentary time <28 h/wk and physical activity ≥30.6 METs-h/wk).

Conclusion:

We could find that the positive association between sedentary time and HOMA-IR, and a negative association between physical activity and HOMA-IR in middle-aged Korean, independently. Compared to the participants with the highest physical activity and the lowest sedentary time, few exceptions, there were significant and positive associations of categories combined with sedentary time and physical activity with insulin resistance. Both sedentary time and physical activity are independently important factors related to insulin resistance.

Keywords: Sedentary time; physical activity; Insulin resistance; HOMA-IR

I. INTRODUCTION

Insulin resistance refers to a decrease in a target cell's metabolic response to insulin, or at the whole-organism level, an impaired lowering effect of circulating or injected insulin on blood glucose. The deterioration of systemic insulin responses related to glucose handling, referred to as insulin resistance, is a serious syndrome associated with health behavior, such as sedentary time, food consumption, and physical activity.[1, 2]

Physical activity has established protective effects on human health, and its potential benefits for the prevention, management, and treatment of cardiovascular diseases (CVD)[3], on the other hand, the sedentary time has not yet been sufficiently studied.[4, 5, 6] In the past, many researchers used to consider physical inactivity as sedentary time, however these days, a consensus is building that sedentary time is distinct from lack of physical activity.[4] The current consensus definition of sedentary time has both an energy expenditure component (≤1.5 METs) and a postural component (sitting, reclining, or lying). [7]

There are several studies about the combined association of sedentary time and physical activity on human health outcomes. One prospective study evaluated that The RRs for increased risk of diabetes in the lowest physical activity and the highest TV watching tertile categories [Risk ratio, 95% CI; 2.89, (2.21-3.79)], RRs for risk

of obesity [RR, 95% CI; 1.90, (1.61-2.24)] compared to reference categories with the highest physical activity and the lowest TV watching time.[8] In the largest study, pooled data on 1,005,791 participants to examine the combined associations of sedentary time and physical activity on mortality from CVD, cancer, and all-causes, and they demonstrated that moderate-to-vigorous physical activity was inversely associated with CVD mortality at every level of sitting (8 hours per day). When considering the associations of sedentary time across different physical activity levels, while the associations between sedentary time and mortality were significant in individuals with the lowest levels of moderate volume physical activity, the relationship between sedentary time and mortality were no longer statistically significant in individuals who were participating in ≥35.5 METs-h/wk of physical activity.[9]

Considering insulin resistance as the outcome, a cross-sectional study in Korea have assessed the effect of physical activity on HOMA-IR and showed that physically inactive (less than of minimum levels of 150 minutes/week moderate activity or less than 75 minutes/week of vigorous physical activity or a combination of both by WHO guidelines[10]) significantly increased the risk for high value of HOMA-IR (1.615[1.104-2.363] vs 1.00 in non-obese).[11] Another study also showed that the sufficiently active group had lower levels of fasting blood glucose and HOMA-IR than the insufficiently active group, and HOMA-IR was negatively correlated with

the total walking activity ($p<0.05$).[12] According to one study in Finland, the greater proportion of the day the subjects spent in sedentary activities, the more insulin resistant they were.[13]

To our knowledge, there are few studies about combined association between sedentary time and physical activity on insulin resistance, especially in Korean adults. Therefore, the main aim of this study was to examine the combined associations between sedentary time and physical activity with insulin resistance in middle-aged Korean adults.

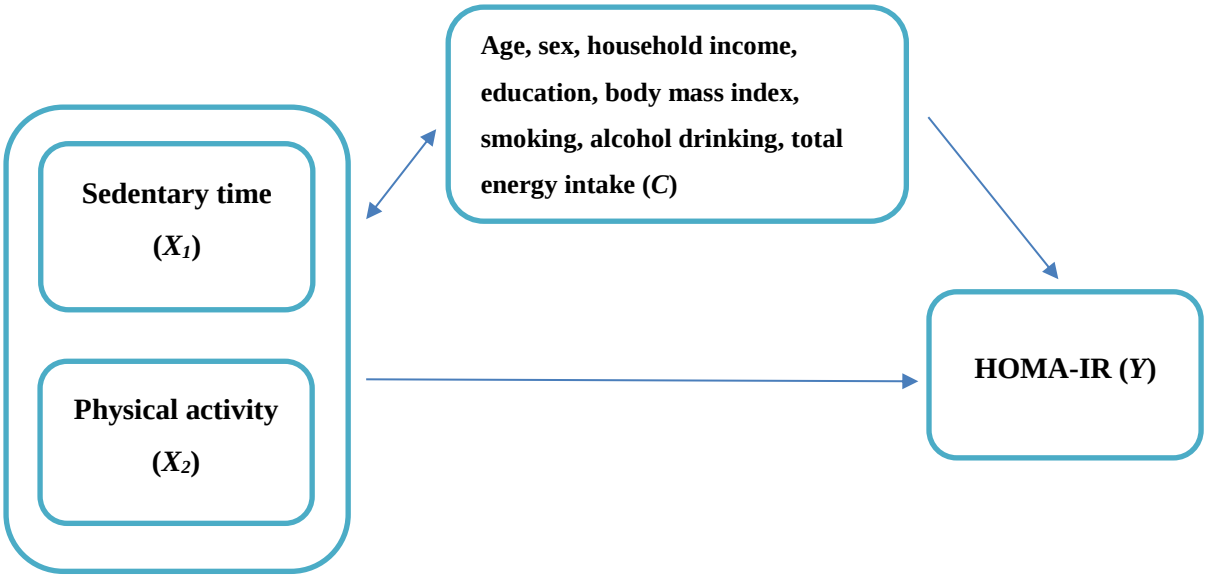


Figure 1. Conceptual diagram of relationships of sedentary time and physical activity (predictors; *X*) with HOMA-IR (outcomes; *Y*) with measured confounders (covariates; *C*).

II. MATERIALS AND METHODS

1. Data source and participants

The present study used baseline data from the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) cohort study operated by the Yonsei University College of Medicine in Seoul, Korea, and Ajou University School of Medicine in Suwon, Korea, a population-based study conducted from December 2013 to February 2018. The inclusion criteria were 1) community-dwelling adults aged 30-64 years, 2) ability to represent their own opinions regarding study participation, 3) no medical history of severe diseases (cancer within two years, myocardial infarction, stroke, heart failure), 4) not participated in any clinical trials, and 5) not pregnant.

The CMERC cohort study enrolled 8,097 participants (mean age at baseline, 51.4 ± 8.7 years; 2,808 men and 5,289 women), the methods of which have been described in detail elsewhere.[14, 15] The current study has conducted in the entire cohort without participants with exclusion criteria. We excluded 3 participants due to missing values on the questionnaire about sedentary time, 4 participants for missing of the laboratory measurements (glucose, insulin), 441 participants who were taking anti-diabetes mellitus medication and a participant with missing for anti-diabetes medication use. Also we excluded 8 participants those who reported

total time for physical activity were more than 16 hours/day because of outliers.[13] Finally, we included 7,640 participants in the analysis (mean age at baseline, 51.2 ± 8.8 years; 2,575 men and 5,065 women) [Figure 2]. Figure 2 shows a flow chart of the determination of the study population. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of Severance Hospital at Yonsei University College of Medicine (Number of Institutional Review Board: 4-2013-0661) and of Ajou University Hospital, Suwon, Korea (AJIRB-BMR-SUR-13-272).

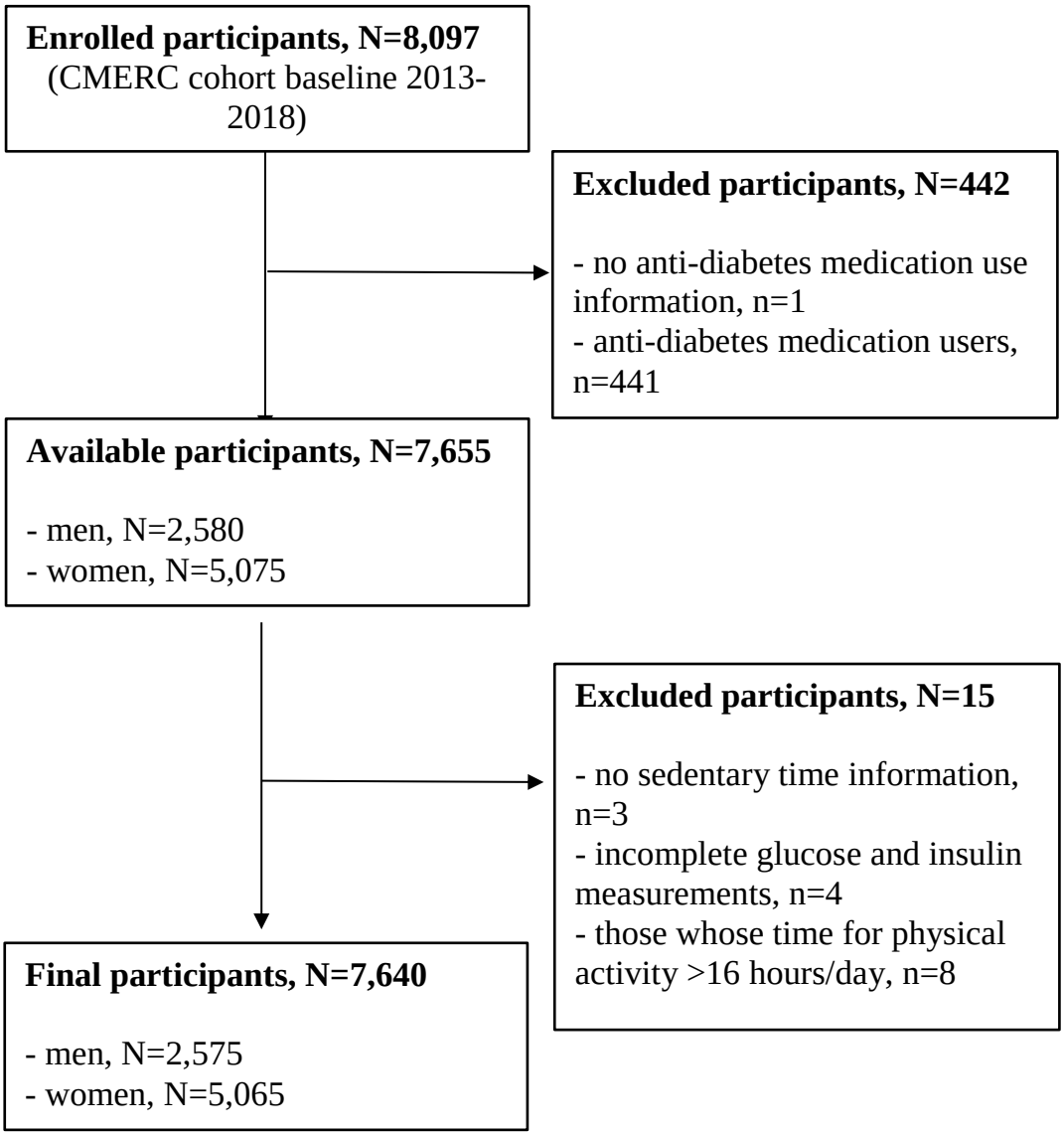


Figure 2. Flow diagram of the study population.

2. MEASUREMENT

(1) Self-reported Sedentary time and physical activity

Sedentary time (defined as requiring fewer or equal than 1.5 METs and having a postural component, such as sitting, reclining, or lying)[7] and physical activity, which was more active than light-intensity activity (1.6 to less than 3.0 METs)[7] were measured using a Korean version of the international physical activity questionnaire-short form. The questionnaire contains questions; “During the last 7 days, how many days did you spend on sedentary behaviors/doing some activities?” and “During the last 7 days, how much time did you usually spend on sedentary behaviors/doing some activities on a day?”. Participants were asked to consider vigorous, moderate-intensity or walking activity time spent for at least 10 minutes continuously in a typical week, for instance, paid or unpaid work, study/training, household chores, fishing, seeking employment etc, in which vigorous-intensity activity causes large increases in breathing or heart rate like carrying or lifting heavy loads or construction work and moderate-intensity activity causes a small increase in breathing or heart rate such as brisk walking, cycling, or swimming.

About sedentary time, participants were asked to consider the sedentary time spent at work and at home, during transportation, lying down or reclining while doing some activities, watching TV, or using a computer to capture all

non-standing spent time while awake.

Data from the IPAQ-SF were summed within each item (i.e., vigorous, moderate, walking) to estimate the total amount of time spent in physical activity per week with bouts of at least 10 min. Physical activity (METs-h/wk) was estimated by summing the product of reported time within each item by an METs value to each category of physical activity and expressed as a weekly average METs score (1 METs = resting energy expenditure) according to the official IPAQ scoring protocol. Vigorous physical activity was assumed to correspond to 8 METs, moderate physical activity to 4 METs, and walking to 3.3 METs.[16] Sedentary time was also estimated by summing total weekly time (hours/week). IPAQ-SF has acceptable validations from other study.[17]

(2) Biochemical Measurements

Venous blood samples were collected following an 8-hour fasting status. All blood samples were delivered to the laboratory center for analysis. Fasting blood glucose levels were measured colorimetrically (ADIVA1800 Auto Analyzer; Siemens Chemistry Calibrator). And fasting insulin levels were determined by an immunoradiometric assay (SR-300; Stratec, Birkenfeld, Germany). Homeostasis model assessment of insulin resistance (HOMA-IR) was used to evaluate insulin resistance with the formula; HOMA-IR = fasting

glucose (mg/dL) x fasting insulin (μIU/mL)/405.[18]

(3) Covariates

In the baseline assessment, the participants were asked with their demographic characteristics, socio-economic status, medical/medication history, and health behavior (smoking, alcohol drinking, and food consumption) by a trained interviewer using a general questionnaire with a standardized protocol. Information on household income was classified into quartiles (<24.0, 24.0-<34.64, 34.64-<48.0, ≥48.0 million Korean Won/year). Educational level was grouped based on the education curriculum in Korea (elementary school or below, middle school or high school, and college or above). Smoking and alcohol drinking status was categorized into “Never”, “Past”, and “Current”. Dietary exposures were evaluated using a semi-quantitative food frequency questionnaire (FFQ). There were 112 food items and dishes, and nine levels of response categories for the frequency and amount of consumption during the preceding year: never, 1 time/month, 2-3 times/month, 1 time/week, 2-4 times/week, 5-6 times/week, 1 time/day, 2 times/day, and 3 times/day. And then, participants were asked to select one of the following three: 0.5, 1.0, and 1.5-2.0 dishes per one intake. The Korean version of the FFQ has acceptable

reproducibility and modest validity.[19] Body mass index (BMI) was calculated as body weight in kilograms divided by standing square height meters.

3. Statistical analysis

(1) Data handling

Sedentary time categorization was the tertiles in our dataset; <28, 28-<49, or ≥49 h/wk, and physical activity was also categorized into tertiles <9.9, 9.9-<30.6, or ≥30.6 METs-h/wk in a similar way as in recent studies.[3, 8, 9, 20, 21] We re-coded time of activity to 'zero' when reported time of a bout of activity was less than 10 minutes according to minimum value for the duration of activity rationale, and we truncated all walking, moderate and vigorous time exceeding 3 hours or 180 minutes/day according to the 'truncation of data rules' for IPAQ-short form. These rule attempted to normalize the distribution of levels of activity which were skewed in a data set.[16] Insulin resistance was evaluated by using HOMA-IR where the values were more than 1.6 based on the Japanese Diabetes Society guidelines.[21]

(2) Data analyses

A chi-square test and generalized linear regression models (GLMs) were used to examine the significance of the differences in variables according to tertile groups of sedentary time. GLMs were used to examine the p-value for the difference of the variance of variables. Continuous variables are shown as mean and standard deviation or median and interquartile range, while categorical variables are shown as frequency and column percentage.

The associations between sedentary time and physical activity with HOMA-IR were analyzed by the multivariate linear regression model. The association of sedentary time and physical activity with insulin resistance and the combined associations between sedentary time and physical activity with insulin resistance were analyzed by the multivariate logistic regression model. We examined the combined associations among nine combined categories in which tertile groups of sedentary time and physical activity were combined; physical activity ≥30.6 METs-h/wk and sedentary time <28 h/wk were served as reference group. Interaction was tested by fitting an interaction term in the analyzed model. We adjusted for age, gender, education, household income, BMI, smoking, alcohol drinking, total energy intake, sedentary time, or physical activity. All tests were performed using the SAS version 9.4 (SAS

Institute, Cary, NC, USA), and statistical significance was defined as a two-sided p-value less than 0.05.

III. RESULTS

1. Characteristics of the study population

The general characteristics of the study population are provided in [Table 1]. In tertile categories of the sedentary time (<28, 28-<49, or ≥49 hours/week), for each item for physical activity, vigorous-intensity activity (VPA) accounted for 22.9%, 22.0%, and 19.6% according to increasing sedentary time categories. Moderate-intensity activity (MPA) was 42.7%, 39.4%, and 35.2% and walking activity was 87.9%, 89.4%, and 86.1% in sedentary categories, respectively.

Women more accounted for 72.6% in the lowest sedentary time (<28 h/wk) group than men (27.4%). In the highest sedentary group, participants who were obese accounted for 37.8%, and it was more portion than in other sedentary time groups.

Table 1. General characteristics of the study population

Characteristics	Sedentary time (h/wk)			*p*-value for difference*
	<28 (n=1,813)	28-<49 (n=3,028)	≥49 (n=2,799)	
Physical activity, METs-h/wk	23.1 [7.7-51.6]	20.0 [7.7-46.2]	14.6 [5.5-32.5]	<.0001
Vigorous-intensity activity, n (%)	416 (22.9)	666 (22.0)	550 (19.6)	
Moderate-intensity activity, n (%)	775 (42.7)	1,194 (39.4)	985 (35.2)	
Walking, n (%)	1,594 (87.9)	2,706 (89.4)	2,411 (86.1)	
HOMA-IR†	1.8 [1.4-2.4]	1.9 [1.4-2.5]	1.9 [1.5-2.6]	<.0001
Age, years	52.0 ± 8.2	52.1 ± 8.4	49.6 ± 9.3	<.0001
Total energy intake, kcal/day	2,290.1 ± 810.7	2,252.4 ± 775.6	2,320.1 ± 841.8	0.010
Sex				<.0001
Men	497 (27.4)	88 (29.1)	1,196 (42.7)	
Women	1,316 (72.6)	2,146 (70.9)	1,603 (57.3)	
Body mass index, kg/m²				<.0001
Underweight (<18.5)	25 (1.4)	57 (1.9)	40 (1.4)	
Normal (18.5-<25.0)	1,202 (66.3)	1,995 (65.9)	1,701 (60.8)	
Obese (≥25.0)	586 (32.3)	976 (32.2)	1,058 (37.8)	
Education				<.0001
None/elementary	148 (8.2)	143 (4.7)	83 (3.0)	
Middle/high school	1,127 (62.2)	1,677 (55.4)	1,203 (43.0)	
University and above	538 (29.7)	1,208 (39.9)	1,512 (54.0)	
Household income‡				<.0001
Low	522 (29.0)	685 (22.7)	531 (19.0)	
Middle-low	505 (28.0)	812 (26.9)	740 (26.5)	
Middle-high	382 (21.2)	690 (22.9)	717 (25.7)	
High	393 (21.8)	828 (27.5)	802 (28.8)	
Smoking status				<.0001
Never smoker	1,344 (74.1)	2,235 (73.8)	1,765 (63.1)	
Former smoker	267 (14.7)	464 (15.3)	587 (21.0)	
Current smoker	202 (11.1)	329 (10.9)	447 (16.0)	
Alcohol consumption				<.0001
Never drinker	483 (26.6)	824 (27.2)	621 (22.2)	
Former drinker	71 (3.9)	94 (3.1)	103 (3.7)	
Current drinker	1,259 (69.4)	2,110 (69.7)	2,075 (74.1)	

Values are presented as mean ± standard deviation, numbers (percent), or median [interquartile range].

*One-way analyses of variance for continuous variables and chi-square tests for categorical variables.

† HOMA-IR (homeostasis model assessment of insulin resistance) was calculated according to the formula; fasting glucose (mg/dL)*fasting insulin (μIU/mL)/405.

‡ Household income was categorized by quartile with <2400, 2400-<3464.1, 3464.1-<4800, 4800+ ten thousand Korean won/year.

2. Association of sedentary time and physical activity with HOMA-IR

Sedentary time as continuous variable was positive associatied with HOMA-IR [β (standard error; SE), p-value; 0.004 (0.001), <.0001] after adjustment age and sex. Its association was still significant after fully adjustment [β (SE), p-value; 0.002 (0.001), <.0001], also physical activity as continuous variable was inversely associated with HOMA-IR in both the sex and age adjusted model and the fully-adjusted model [β (SE), p-value; -0.002 (0.000), <.0001], independently each other [Table 2].

Examining the associations between categories of sedentary time and physical activity with HOMA-IR in the fully adjusted model, increasing sedentary time were statistically significant associated with increasing HOMA-IR [β (SE), p-value; 0.131 (0.032), <.0001 in the 28-<49 h/wk, and 0.144 (0.033), <.0001 in ≥49 h/wk sedentary time category compared to reference group (<28 h/wk sedentary time], and the less physical activity, the higher values of HOMA-IR were found in the fully adjusted model; [β (SE), p-value; 0.084 (0.030), 0.005 in 9.9-<30.6 METs-h/wk, and [β (SE), p-value; 0.211 (0.030), <.0001] in <9.9 METs-h/wk physical activity category compared to reference group (<9.9 METs-h/wk physical activity]. Either categories of physical activity or

sedentary time were independently associated with HOMA-IR. Obese participants had a higher mean value of HOMA-IR than the normal BMI group [β (SE), p-value; 0.819 (0.026), <.0001]. Current or former drinkers had less mean value of HOMA-IR than never drinker [β (SE), p-value; -0.191 (0.070), 0.007 in former drinker, and -0.119 (0.030), <.0001 in current drinker, repectvely] [Table 3].

About combined associations between sedentary time and physical activity with HOMA-IR, a positive linear trend was found compared to the reference group (sedentary time <28h/wk and physical activity ≥30.6 METs-h/wk) in both adjusted models [p for trend as a continuous form in GLMs; <.0001]. When the highest sedentary time (≥49 h/wk) and the lowest physical activity (<9.9 METs-h/wk), the combined association with HOMA-IR was [β (SE), p-value; 0.421 (0.052), <.0001] [Table 4].

Table 2. Association of sedentary time and physical activity as continuous variables with HOMA-IR†

Variables	Number of people	Sex and age adjusted model			Sex and age adjusted model			Fully adjusted model‡		
		β	Standard Error	*p*-value	B	Standard Error	*p*-value	β	Standard Error	*p*-value
Sedentary time, hours/week	7,640	0.004	0.001	<.0001				0.002	0.001	<.0001
Physical activity, METs-hours/week	7,640				-0.002	0.000	<.0001	-0.002	0.000	<.0001
Age	7,640	0.003	0.001	0.031	0.003	0.001	0.031	0.001	0.002	0.395
Total energy intake, kcal/day	6,823							0.000	0.000	0.379
Sex										
Men	2,575		Reference			Reference			Reference	
Women	5,065	-0.311	0.026	<.0001	-0.311	0.026	<.0001	-0.110	0.040	0.006
Body mass index, kg/m²										
Underweight (<18.5)	122							-0.404	0.097	<.0001
Normal (18.5-<25.0)	4,898								Reference	
Obese (≥25.0)	2,620							0.820	0.026	<.0001
Education										
None/elementary	374							-0.006	0.064	0.923
Middle/high school	4,007							0.021	0.027	0.431
University and above	3,258								Reference	
Household income⁋										
Low	1,738								Reference	
Middle-low	2,057							-0.012	0.035	0.741
Middle-high	1,789							0.004	0.036	0.906
High	2,023							0.050	0.036	0.164
Smoking										
Never smoker	5,344								Reference	
Former smoker	1,318							0.029	0.044	0.505
Current smoker	978							0.018	0.048	0.711
Alcohol drinking										
Never drinker	1,928								Reference	
Former drinker	268							-0.197	0.07	0.005
Current drinker	5,444							-0.125	0.03	<.0001

† HOMA-IR (homeostasis model assessment of insulin resistance) was calculated according to the formula; fasting glucose (mg/dL)*fasting insulin (μIU/mL)/405.

‡ Full-model was adjusted for age, sex, household income, education, body mass index, smoking, alcohol drinking, total energy intake, and sedentary time or physical activity

⁋ Household income was categorized by quartile with <2400, 2400-<3464.1, 3464.1-<4800, 4800+ ten thousand Korean won/year.

Table 3. Association of sedentary time and physical activity as continuous variables with HOMA-IR†

Variables	Number of people	Sex and age adjusted model			Sex and age adjusted model			Fully adjusted model‡		
		β	Standard Error	*p*-value	β	Standard Error	*p*-value	β	Standard Error	*p*-value
Sedentary time, hours/week										
<28	1,813		Reference						Reference	
28-<49	3,028	0.114	0.032	0.000				0.131	0.032	<.0001
≥49	2,799	0.178	0.033	<.0001				0.144	0.033	<.0001
Physical activity, METs-hours/week										
≥30.6	2,563					Reference			Reference	
9.9-<30.6	2,486				0.101	0.030	0.001	0.084	0.030	0.005
<9.9	2,591				0.250	0.030	<.0001	0.211	0.030	<.0001
Total energy intake, kcal/day	6,823							0.000	0.000	0.529
Age	7,640	0.003	0.001	0.020	0.004	0.001	0.008	0.002	0.002	0.318
Sex										
Men	2,575		Reference			Reference			Reference	
Women	5,065	-0.275	0.026	<.0001	-0.311	0.026	<.0001	-0.116	0.040	0.004
Body mass index, kg/m²										
Underweight (<18.5)	122							-0.416	0.097	<.0001
Normal (18.5-<25.0)	4,898								Reference	
Obese (≥25.0)	2,620							0.819	0.026	<.0001
Education										
None/elementary	374							-0.024	0.065	0.714
Middle/high school	4,007							0.010	0.027	0.714
University and above	3,258								Reference	
Household income⁋										
Low	1,738								Reference	
Middle-low	2,057							-0.010	0.035	0.777
Middle-high	1,789							0.005	0.036	0.895
High	2,023							0.052	0.036	0.142
Smoking										
Never smoker	5,344								Reference	
Former smoker	1,318							0.031	0.044	0.479
Current smoker	978							0.013	0.048	0.788
Alcohol drinking										
Never drinker	1,928								Reference	
Former drinker	268							-0.191	0.070	0.007
Current drinker	5,444							-0.119	0.030	<.0001

† HOMA-IR (homeostasis model assessment of insulin resistance) was calculated according to the formula; fasting glucose (mg/dL)*fasting insulin (μIU/mL)/405.

‡ Full-model was adjusted for age, sex, household income, education, body mass index, smoking, alcohol drinking, total energy intake, and sedentary time or physical activity

⁋ Household income was categorized by quartile with <2400, 2400-<3464.1, 3464.1-<4800, 4800+ ten thousand Korean won/year.

Table 4. Combined associations of sedentary time (ST) and physical activity (PA) with HOMA-IR†

Variables	Number of people	Sex and age adjusted model			Fully adjusted model‡		
		β	Standard Error	*p*-value	β	Standard Error	*p*-value
Combined categories⁋							
ST<28 and PA≥30.6	736		Reference			Reference	
28≤ST<49 and PA≥30.6	1,087	0.159	0.051	0.002	0.193	0.051	0.000
ST≥49 and PA≥30.6	740	0.188	0.056	0.001	0.162	0.056	0.004
ST<28 and 9.9≤PA<30.6	512	0.250	0.062	<.0001	0.208	0.062	0.001
28≤ST<49 and 9.9≤PA<30.6	1,005	0.216	0.052	<.0001	0.230	0.052	<.0001
ST≥49 and 9.9≤PA<30.6	969	0.213	0.052	<.0001	0.232	0.053	<.0001
ST<28 and PA<9.9	565	0.187	0.060	0.002	0.201	0.060	0.001
28≤ST<49 and PA<9.9	936	0.370	0.053	<.0001	0.358	0.053	<.0001
ST≥49 and PA<9.9	1,090	0.466	0.051	<.0001	0.421	0.052	<.0001
Total energy intake, kcal/day	6,823				0.000	0.000	0.491
Age	7,640	0.004	0.001	0.004	0.001	0.002	0.337
Sex							
Men	2,575		Reference			Reference	
Women	5,065	-0.298	0.026	<.0001	-0.116	0.040	0.004
Body mass index, kg/m²							
Underweight (<18.5)	122				-0.415	0.097	<.0001
Normal (18.5-<25.0)	4,898					Reference	
Obese (≥25.0)	2,620				0.818	0.026	<.0001
Education							
None/elementary	374				-0.021	0.064	0.743
Middle/high school	4,007				0.011	0.027	0.673
University and above	3,258					Reference	
Household income⁑							
Low	1,738					Reference	
Middle-low	2,057				-0.008	0.035	0.814
Middle-high	1,789				0.007	0.036	0.854
High	2,023				0.053	0.036	0.139
Smoking							
Never smoker	5,344					Reference	
Former smoker	1,318				0.034	0.044	0.435
Current smoker	978				0.012	0.048	0.799
Alcohol drinking							
Never drinker	1,928					Reference	
Former drinker	268				-0.195	0.070	0.006
Current drinker	5,444				-0.120	0.030	<.0001

† HOMA-IR (homeostasis model assessment of insulin resistance) was calculated according to the formula; fasting glucose (mg/dL)*fasting insulin (μIU/mL)/405.

‡ Fully adjusted model was adjusted for age, sex, household income, education, body mass index, smoking, alcohol drinking, and total energy intake

⁋ Sedentary time (hours/week) and physical activity (METs-hours/week) were combined as nine categories.

⁑ Household income was categorized by quartile with <2400, 2400-<3464.1, 3464.1-<4800, 4800+ ten thousand Korean won/year.

3. Association of sedentary time and physical activity with insulin resistance

Table 5 presents the associations between sedentary time categories (<28, 28-<49, or ≥49 h/wk) and physical activity categories (<9.9, 9.9-<30.6, or ≥30.6 METs-h/wk) with insulin resistance. The participants who had equal or more than 49 h/wk sedentary time had 1.24 times sinificant increased odds ratio [CI; 1.07-143 in the fully adjusted model] for insulin resistance, and who had more than 28 h/wk and less than 49 h/wk sedentary time had 1.11 times higher but not significant [CI; 0.97-1.28] compared to the reference group (sedentary time <28 h/wk and physical activity ≥30.6). The association of increasing odds ratio of insulin resistance according to decreasing categories in physical activity was also clearly found [OR (95% CI); 1.30 (1.15-1.49) in a group with 9.9-<30.6 METs-h/wk, 1.67 (1.46-1.91) in a group with <9.9 METs-h/wk] [Table 5].

When observing combined associations between sedentary time and physical activity with insulin resistance, few exceptions, there were significantly increasing association between combined categories and insulin resistance (p for trend; <.0001, p for interaction; 0.394). The estimates of combined group with highest sedentary time (≥49 h/wk) and the lowest physical activity (<9.9 METs-h/wk) for insulin resistance were highest in combined categories [OR

(95% CI); 2.20 (1.75-2.77)] compared to reference group [Table 6]. The combined associations between sedentary time and physical activity with insulin resistance were represented as a figure to observe them clearly. As seen in the figure, when physical activity ≥30.6 METs-h/wk, there were no significant associations between combined categories with insulin resistance, and when physical activity was less than 30.6 METs-h/wk, there were significant and positive associations between combined categories with insulin resistance [Figure 3]. As for combined associations, we also conducted sensitivity analysis among combinations with two categories based on meidan or tertiles of sedentary time and physical activity with insulin resistance in fully adjusted model, and the sensitivity results were few different with our main results. [Appendix 1] [Appendix 2]. And we also evaluated insulin resistance with 2.5 cut-off for HOMA-IR, and the results were similar to our main results [Appendix 3].

Table 5. Association of sedentary time and physical activity with insulin resistance†

Variables	Number of people	Number of people (%) with insulin resistance	Sex and age adjusted model		Sex and age adjusted model		Fully adjusted model‡	
			OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Sedentary time, hours/week								
<28	1,813	1,124 (62.0)	1.00	Reference			1.00	Reference
28-<49	3,028	1,963 (64.8)	1.12	(0.99-1.27)			1.11	(0.97-1.28)
≥49	2,799	1,933 (69.1)	1.33	(1.17-1.51)			1.24	(1.07-1.43)
Physical activity, METs-hours/week								
≥30.6	2,563	1,554 (60.6)			1.00	Reference	1.00	Reference
9.9-<30.6	2,486	1632 (65.6)			1.31	(1.17-1.47)	1.30	(1.15-1.49)
<9.9	2,591	1834 (70.8)			1.70	(1.51-1.91)	1.67	(1.46-1.91)
Total energy intake, kcal/day	6,823	4,568 (67.0)					1.00	(1.00-1.00)
Age	7,640	5,020 (65.7)	1.01	(1.01-1.02)	1.01	(1.01-1.02)	1.01	(1.00-1.02)
Sex								
Men	2,575	1,839 (71.4)	1.00	Reference	1.00	Reference	1.00	Reference
Women	5,065	3,181 (62.8)	0.69	(0.62-0.76)	0.63	(0.57-0.70)	0.86	(0.72-1.03)
Body mass index, kg/m²								
Underweight (<18.5)	122	36 (29.5)					0.29	(0.19-0.44)
Normal (18.5-<25.0)	4,898	2,768 (56.5)					1.00	Reference
Obese (≥25.0)	2,620	2,216 (84.6)					4.04	(3.54-4.61)
Education								
None/elementary	374	253 (67.6)					1.02	(0.76-1.37)
Middle/high school	4,007	2,640 (65.9)					1.03	(0.91-1.16)
University and above	3,258	2,126 (60.3)					1.00	Reference
Household income⁋								
Low	1,738	1,114 (64.1)					1.00	Reference
Middle-low	2,057	1,320 (64.2)					0.96	(0.83-1.12)
Middle-high	1,789	1,177 (65.8)					1.07	(0.91-1.25)
High	2,023	1,385 (68.5)					1.19	(1.02-1.39)
Smoking								
Never smoker	5,344	3,414 (63.9)					1.00	Reference
Former smoker	1,318	921 (69.9)					0.99	(0.81-1.20)
Current smoker	978	385 (39.4)					1.06	(0.85-1.31)
Alcohol drinking								
Never drinker	1,928	1,290 (66.9)					1.00	Reference
Former drinker	268	164 (61.2)					0.67	(0.49-0.90)
Current drinker	5,444	3,566 (65.5)					0.79	(0.70-0.91)

† Insulin resistance was evaluated with a high value of HOMA-IR >1.6.

‡ Fully adjusted model was adjusted for age, sex, household income, education, body mass index, smoking, alcohol drinking, total energy intake, and sedentary time or physical activity.

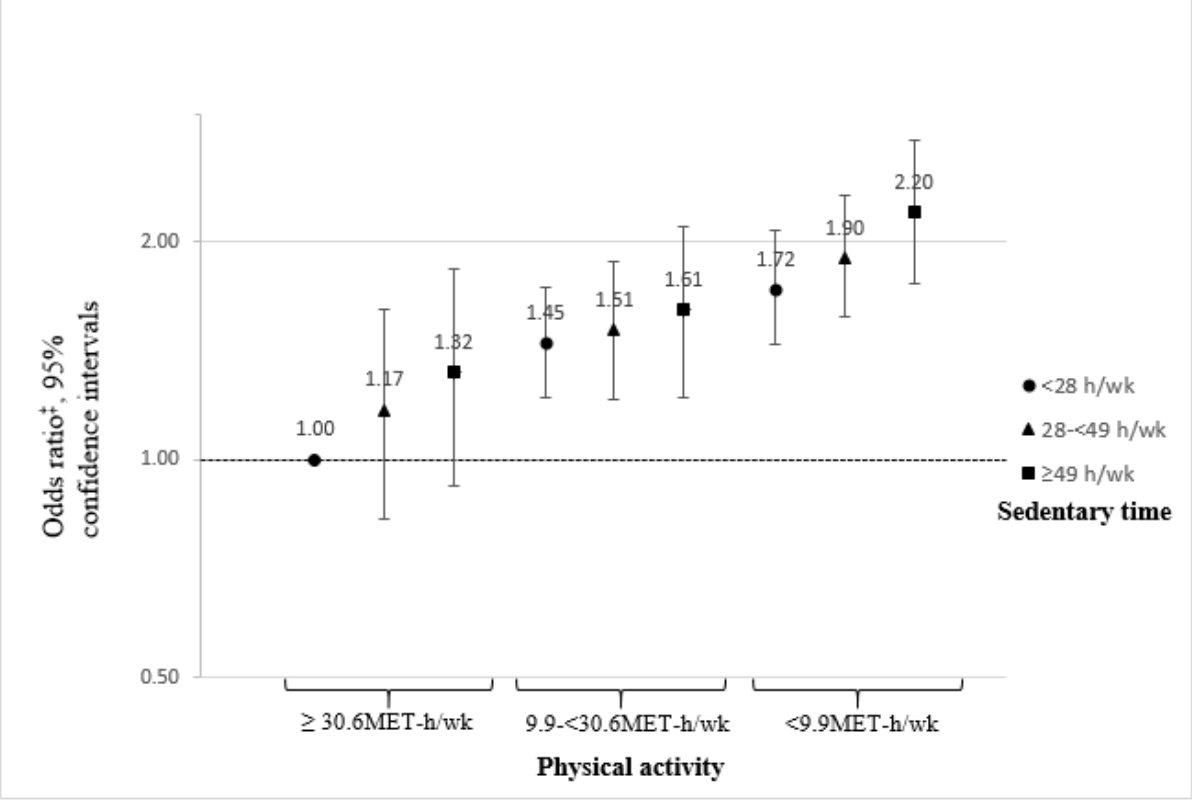
⁋ Household income was categorized by quartile with <2400, 2400-<3464.1, 3464.1-<4800, 4800+ ten thousand Korean won/year.

Table 6. Combined associations of sedentary time (ST) and physical activity (PA) with insulin resistance†

Variables	Number of people	Number of people (%) with insulin resistance	Sex and age adjusted model		Fully adjusted model‡	
			OR	(95% CI)	OR	(95% CI)
Combined categories⁋						
ST<28 and PA≥30.6	736	415 (56.4)	1.00	Reference	1.00	Reference
28≤ST<49 and PA≥30.6	1,087	648 (59.6)	1.13	(0.94-1.37)	1.17	(0.94-1.45)
ST≥49 and PA≥30.6	740	491 (66.4)	1.45	(1.17-1.80)	1.32	(1.04-1.67)
ST<28 and 9.9≤PA<30.6	512	334 (65.2)	1.54	(1.21-1.94)	1.45	(1.11-1.89)
28≤ST<49 and 9.9≤PA<30.6	1,005	657 (65.4)	1.52	(1.25-1.85)	1.51	(1.21-1.88)
ST≥49 and 9.9≤PA<30.6	969	641 (66.2)	1.54	(1.26-1.88)	1.62	(1.29-2.03)
ST<28 and PA<9.9	565	375 (66.4)	1.64	(1.31-2.07)	1.72	(1.32-2.23)
28≤ST<49 and PA<9.9	936	658 (70.3)	1.96	(1.60-2.40)	1.90	(1.51-2.39)
ST≥49 and PA<9.9	1,090	801 (73.5)	2.24	(1.83-2.73)	2.20	(1.75-2.77)
Total energy intake, kcal/day	6,823	4,568 (67.0)			1.00	(1.00-1.00)
Age	7,640	5,020 (65.7)	1.01	(1.01-1.02)	1.01	(1.00-1.02)
Sex						
Men	2,575	1,839 (71.4)	1.00	Reference	1.00	Reference
Women	5,065	3,181 (62.8)	0.65	(0.59-0.72)	0.86	(0.72-1.03)
Body mass index, kg/m²						
Underweight (<18.5)	122	36 (29.5)			0.29	(0.19-0.44)
Normal (18.5-<25.0)	4,898	2,768 (56.5)			1.00	Reference
Obese (≥25.0)	2,620	2,216 (84.6)			4.03	(3.53-4.61)
Education						
None/elementary	374	253 (67.6)			1.02	(0.76-1.37)
Middle/high school	4,007	2,640 (65.9)			1.03	(0.91-1.16)
University and above	3,258	2,126 (60.3)			1.00	Reference
Household income⁑						
Low	1,738	1,114 (64.1)			1.00	Reference
Middle-low	2,057	1,320 (64.2)			0.96	(0.83-1.12)
Middle-high	1,789	1,177 (65.8)			1.07	(0.91-1.25)
High	2,023	1,385 (68.5)			1.19	(1.02-1.39)
Smoking						
Never smoker	5,344	3,414 (63.9)			1.00	Reference
Former smoker	1,318	921 (69.9)			0.99	(0.81-1.20)
Current smoker	978	385 (39.4)			1.06	(0.85-1.31)
Alcohol drinking						
Never drinker	1,928	1,290 (66.9)			1.00	Reference
Former drinker	268	164 (61.2)			0.66	(0.49-0.90)
Current drinker	5,444	3,566 (65.5)			0.79	(0.69-0.91)

† Insulin resistance was evaluated with a high value of HOMA-IR >1.6.
‡ Fully adjusted model was adjusted for age, sex, household income, education, body mass index, smoking, alcohol drinking, and total energy intake.
⁋ Sedentary time (hours/week) and physical activity (METs-hours/week) were combined as nine categories.
⁑ Household income was categorized by quartile with <2400, 2400-<3464.1, 3464.1-<4800, 4800+ ten thousand Korean won/year.

Figure 3. Combined associations of sedentary time and physical activity with insulin resistance†



Physical activity (≥30.6 MET-h/wk) and sedentary time (<28 h/wk) combination was served as a reference group.

† Insulin resistance was defined as high value of HOMA-IR >1.6.

‡ Odds ratio for insulin resistance in model full-adjusted for age, sex, household income, education, body mass index, smoking, alcohol drinking, and total energy intake.

Ⅳ. DISCUSSION

1. Summary of findings

This study examined the association between sedentary time and physical activity with HOMA-IR or insulin resistance and combined associations between sedentary time and physical activity with HOMR-IR or insulin resistance using nationally represented data. Overall, sedentary time was positively associated with HOMA-IR, and physical activity was inversely associated with HOMA-IR, independently. When we combined the sedentary time and physical activity with each tertile group, in physical activity ≥30.6 METs-h/wk, there were no significant associations between combined categories with insulin resistance. However, those who had less than 30.6 METs-h/wk physical activity were significant and positively associated with insulin resistance.

2. Comparison with previous studies

Our results were similar with several previous studies on other health outcomes. Hu B. et al.[22] researchers studied 37,918 men aged 40 to 75 years and free of diabetes, CVD, and cancer represented that the relative risks (RRs)

for type 2 diabetes across combination with quintiles of physical activity and quartiles of average time spent watching TV. Comparing reference group (physical activity≥46.0 METs-h/wk and sitting time≤3.5 h/wk), those who were in the least active (<10 METs-h/wk) and most sedentary category (>15 h/wk) had a significantly increased risk for type 2 diabetes (RR, 2.92; 95% CI, 1.87-4.55; p for interaction, .90), and the researchers observed independent effect of TV watching and physical activity levels. A prospective cohort study[8], we mentioned earlier in this paper, including 50,227 women (free from diabetes) also showed the independent effects of TV watching and exercise levels on obesity and type 2 diabetes. Compared with women who were in the most active (the highest tertile of METs/wk) and the lowest TV watching category (<6 h/wk), those who were in the lowest of METs per week and most sedentary category (≥20 h/wk) had a significantly increased risk of obesity (RR, 1.90; 95% CI, 1.61-2.24) and type 2 diabetes (RR, 2.89; 95% CI, 2.21-3.79). Compared to other results of the previous studies, a meta-analysis of epidemiological studies reported a summary HR associated with the sedentary time of 1.46 (95% CI, 1.22-1.75) in those with low levels of physical activity versus a HR of 1.16 (95% CI, 0.84-1.59) in those with high levels of physical activity. In summary, high levels of physical activity appear to attenuate the

negative cardiovascular consequences of sedentary time, but more research is required to determine the interactions between physical activity and sedentary time on health outcomes.[23] According to other studies, compared with participants who were persistently inactive, those who increased physical activity had a lower relative risk for having impaired glucose metabolism (relative risk, 0.47; 95% CI, 0.29-0.76).[24] And other study mentioned that physical inactivity is closely associated with metabolic disorders, such as impaired glucose metabolism, which substantially increases risk of cardiovascular disease (CVD).[25] Insulin resistance promotes glucose intolerance and type 2 diabetes with associated comorbidities and also increases the risk of cancer.[1] Hence, our results might help explaining that sedentary time and physical activity could affect the insulin resistance pathway, even to obesity or type 2 diabetes.[26]

3. Possible mechanisms

Hu FB et al.[8] mentioned some potential mechanisms for the observed positive association between sedentary time (including TV watching) and obesity and diabetes risk. They mentioned that sedentary time typically displaces physical activity and thus reduces energy expenditure. Furthermore, sedentary time results in increased food and total energy intake and also tended to follow an

unhealthy eating pattern. Others conducted experimental study that using hinlimb suspension in a rat to mimic human SB, a decrease in lipoprotein lipase activity (the enzyme, a role for hydrolysis of triglyceride-rich lipoproteins), triglyceride uptake into red skeletal muscle, and HDL (high-density lipoprotein)[27] cholesterol concentration were found.[28] Experimental studies have also provided evidence of greater postprandial glucose and insulin level during bouts of prolonged sitting compared with individuals taking frequent standing or walking breaks.[29] Compared with prolonged sitting, breaking up sedentary time with intermittently light-intensity activity can increase anti-inflammatory and antioxidative pathway modulators as well as regulators of glucose tranporter type 4 translocation[30], which reach the surface membrane in skeletal muscle and increase glucose uptake from the circulation.[1] While these studies suggest potential mechanisms involved in sedentary time and physical activity, and more research is needed to determine the pathophysiological pathways through which sedentary time/physical activity impacts risk for CVD.[5, 31]

4. Strengths and Limitations

The strengths of this study include its relatively large sample size (N=7,640) and various confounders. And the results that the combined associations of

physical activity and sedentary time with insulin resistance are scarce, especially in Korea. Hence, our results would be one of the pieces of evidence for the combined association of sedentary time and physical activity with insulin resistance in middle-aged Korean.

Several limitations should be considered when interpreting the results of this study. First of all, our data from sedentary time and physical activity were self-reported based, so measurement error could be in this study. Although the self-reported physical activity estimates could be over-estimated than objectively measuring physical activity and could be under-estimated when measuring sedentary time, the validity was proven by using the IPAQ materials.[17] Second, about physical activity, we couldn't consider types, such as aerobic or muscle-strengthening exercise because of our data limitation. And about sedentary time, we couldn't consider the duration of bouts of sitting, and whether he or she takes some breaks in a bout of sitting[32] also due to data limitation. Third, this study was a cross-sectional design, so temporal causality between sedentary time and physical activity with insulin resistance could not be assessed. Lastly, there are some residual confounding factors, such as; mobility impairment, stress, and employment status etc.[33, 34]

V. CONCLUSIONS

We could find that the positive association between sedentary time and HOMA-IR, and a negative association between physical activity and HOMA-IR in middle-aged Korean, independently. Compared to the participants with the highest physical activity and the lowest sedentary time, with few exceptions, there was significant and positive association of categories combined with sedentary time and physical activity with insulin resistance. Both sedentary time and physical activity are independently important factors related to insulin resistance.

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APPENDIX

Appendix 1. Combined associations between sedentary time and physical activity with insulin resistance (categorized based on the median)

Physical activity	Sedentary time, hours/week					
	<35			≥35		
	n	n (%) of IR*	OR (95% CI)	n	n (%) of IR*	OR (95% CI)
(METs-hours/week)						
≥18.2	1,590	945(59.3)	1.00 (Reference)	2,229	1,420(63.7)	1.19 (1.02-1.38)
<18.2	1,295	858(66.3)	1.54 (1.29-1.83)	2,526	1,800(71.3)	1.77 (1.52-2.06)

Values were analyzed with logistic regression model adjusted for age, sex, household income, education, body mass index, smoking, alcohol drinking, total energy intake

*n for IR; number of people with insulin resistance

Appendix 2. Combined associations between sedentary time and physical activity with insulin resistance (categorized with quartiles)

Physical activity	sedentary time, hours/week											
	<28			28-<35			35-<56			≥56		
	n	n (%) of IR*	OR (95% CI)	n	n (%) of IR*	OR (95% CI)	n	n (%) of IR*	OR (95% CI)	n	n (%) of IR*	OR (95% CI)
MET-hours/week												
≥41.8	576	315 (54.7)	1.00 (Reference)	308	173 (56.2)	1.09 (0.79-1.49)	610	368 (60.3)	1.24 (0.96-1.62)	410	277 (67.6)	1.43 (1.06-1.93)
18.2-<41.8	421	274 (65.1)	1.44 (1.07-1.93)	285	181 (63.5)	1.39 (1.00-1.92)	634	402 (63.4)	1.54 (1.19-2.01)	575	372 (64.7)	1.45 (1.11-1.9)
6.6-<18.2	442	284 (64.3)	1.71 (1.27-2.31)	253	168 (66.4)	1.86 (1.31-2.65)	641	435 (67.9)	1.82 (1.4-2.38)	725	528 (72.8)	2.34 (1.8-3.06)
<6.6	374	251 (67.1)	1.82 (1.33-2.48)	226	155 (68.6)	1.99 (1.38-2.88)	483	341 (70.6)	1.91 (1.43-2.55)	677	496 (73.3)	2.33 (1.77-3.05)

Values were analyzed with logistic regression model adjusted for age, sex, household income, education, body mass index, smoking, alcohol drinking, total energy intake

* n for IR; number of people (proportion) with insulin resistance

Appendix 3. Combined associations between sedentary time and physical activity with insulin resistance (>2.5 cut-off)

Physical activity	Sedentary time, hours/week									
	<28			28≤to<49			≥49			
	n	n (%) of IR*	OR (95% CI)	n	n (%) of IR*	OR (95% CI)	n	n (%) of IR*	OR (95% CI)
(METs-hours/week)									
≥30.6	740	136 (18.4)	1.00 (Reference)	1,090	242 (22.2)	1.25 (0.96-1.64)	741	203 (27.4)	1.38 (1.04-1.83)
9.9-<30.6	512	123 (24.0)	1.19 (0.85-1.68)	1,005	235 (23.4)	1.24 (0.92-1.67)	969	239 (24.7)	1.28 (0.95-1.73)
<9.9	565	135 (23.9)	1.28 (0.91-1.80)	936	276 (29.5)	1.66 (1.22-2.26)	1,090	347 (31.8)	1.67 (1.23-2.27)

Values were analyzed with logistic regression model adjusted for age, sex, household income, education, body mass index, smoking, alcohol drinking, total energy intake

*n for IR; number of person with insulin resistance

ABSTRACT(KOREAN)

중년 한국인의 앉아있는 시간과 신체활동의 인슐린저항성과의 연관성: 심혈관 대사질환 원인 연구센터 연구

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배경 및 목적:
앉아있는 시간과 중등도이상의 신체활동 시간이 인슐린저항성에 미치는 결합효과에 대해서는 잘 알려져 있지 않다. 이 연구의 목적은 앉아있는 시간과 신체활동 시간이 인슐린저항성에 미치는 결합효과를 조사하는 것이다.

연구 방법:
본 단면연구는 심혈관대사질환원인 연구등록(2013 년 12 월부터 2018 년 2 월까지)때의 만 30 세부터 64 세까지의 총 7,640 명(남자 2,575, 여자 5,065 명)의 대상자를 대상으로 연구하였다. 국제 신체활동 설문지-한국형 단축형 한국판을 이용하여 측정된 앉아있는 시간과 신체활동 시간(<28, 28-<49, ≥49 시간/주)와 <9.9, 9.9-<30.6, ≥30.6 METs-시간/주, 여기서 METs-시간/주는 대사성 신진대사율)의 3 분위로 구분되었고 인슐린

저항성은 항상성모형평가 (HOMA-IR)으로 평가 되었다. 여러 공변량을 보정한 뒤 앉아있는 시간과 신체활동 시간 그리고 인슐린저항성 (HOMA-IR>1.6 로 평가함)의 관련성을 다중회귀모델과 다중로지스틱모델로 분석하였다.

연구 결과:

HOMA-IR 과 연속변수로서의 앉아있는 시간은 [측정치 (표준편차), p-값; 0.002 (0.000), <.0001]의 양의 관련성을 보였다. 신체활동은 [측정치 (표준편차), p-값; -0.002 (0.000), <.0001)의 음의 연관성을 나타내었다. 앉아있는 시간과 신체활동의 조합된 그룹에서의 HOMA-IR 와의 관련성은 전반적으로 양의 관련성을 나타내었다 [경향성 p-값; <.0001]. 앉아있는 시간이 가장 많고 (≥49 시간/주) 가장 적은 신체활동 (<9.9 METs-시간/주)을 가진 그룹에서는 인슐린저항성에 대해 [오즈값 (95% 신뢰구간); 2.20 (1.75-2.77), 경향성 p-값; <.0001]의 높은 양의 관련성을 나타내었다.

결론 및 고찰:

우리의 연구결과는 한국의 중년층에서는 앉아서 생활하는 시간과 HOMA-IR 사이의 양의 연관성과 신체 활동 및 HOMA-IR 간의 음의 연관성이 독립적으로 나타난다는 것을 알 수 있었다. 인슐린저항성에 대해 신체활동이 가장 높고 앉아있는 시간이 가장 적은 사람들에 비해, 소수의 예외를 제외하고는, 앉아있는 시간과 신체활동의 조합을 통해 본 관련성은 유의한 양의 연관성을 나타내었다. 앉아서 하는 시간과 신체 활동 모두 인슐린 저항성과 관련된 독립적으로 중요한 요소들이다.

핵심어: 앉아있는 시간; 신체활동; 인슐린 저항성; HOMA-IR