Improvement of physical activity was significantly reduced serum hepatocyte growth factor levels in a general population: 10-year prospective study

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Abstract

Background: We have previously reported that hepatocyte growth factor (HGF) levels were significantly associated with insulin resistance or components of the metabolic syndrome. However, it has been unknown how physical activity (PA) affects HGF levels after a long-term follow-up. Aims: Our aim was to clarify the association between PA changes and HGF levels /cerebro-cardiovascular disease (CVD) development during 10 years follow-up period in a community-dwelling Japanese general population. Methods: Of 1,320 subjects who received a health check-up examination in Tanushimaru town in 1999, 903 subjects (341 males and 562 females) were enrolled, who received the examination both in 1999 and 2009. We evaluated their PA levels by Baecke questionnaire in 1999 and evaluated their PA levels by a simple questionnaire in 2009. We measured the serum HGF levels by ELISA method in 1999 and 2009. We divided into four physical activity groups such as stable low PA, increased PA, decreased PA, and stable high PA. Using these questionnaires, we compared their PA and HGF levels in 10 years. Results: A significant inverse association was found between PA changes and serum HGF levels in 10 years after adjustment for age and sex. The serum HGF levels of increased PA group were significantly lower than stable low PA (p=0.038), and the former group showed the reduced CVD development compared to the latter group after adjustment for age and sex (p=0.012). Conclusions: Our data demonstrated that improvement of PA levels was associated with reduced HGF levels and CVD development.

Introduction

Hepatocyte growth factor (HGF), discovered in 1984 [1], was purified and isolated in 1986 [2]. We have previously reported that serum HGF levels were strongly associated with the metabolic syndrome [3] and the development of insulin resistance [4]. In a sense, serum HGF has been recognized as a marker of metabolic syndrome. On the other hand, regular physical activity (PA) can reduce weight and blood pressure, and also can improve lipid disorders, including elevating high density lipoprotein cholesterol (HDL-C) and lowering triglycerides [5,6], which also improves the insulin resistance [7,8]. However, the impact of PA on serum HGF levels is still unclear. Therefore, in the present study, we examined the relationship between changes of PA and serum HGF levels during 10 years follow-up. Moreover, we also examined that the effects of PA improvement on the serum HGF levels in a community-dwelling Japanese general population.

Materials And Methods

Study population

A periodic epidemiologic survey was performed in 1999 and 2009 in a rural farming community located in south-western Japan (Tanushimaru town). Tanushimaru study was a Japanese cohort of the Seven Countries Study [9]. As previously reported, the demographic characteristics of the residents of this area were similar to those of the general Japanese population [10]. We performed epidemiological studies in every 10 years and followed up the participants every year.

In 1999, the total population aged over 40 years in this district was 3,463 (48.2% of men and 62.0% of women). A total of 1,920 subjects (794 males and 1,126 females; aged 40-95 years) were enrolled in this study. PA was measured by the Baecke PA questionnaire (BPAQ) [11-13], and the HGF levels were measured by ELISA method. In 2009, we measured PA by a simple questionnaire, and the HGF levels were measured again using ELISA method.

Baecke PA questionnaire (BPAQ)

We measured PA by BPAQ in 1999. The questionnaire consists of 16 questions organized into three sections: PA at work (Questions 1-8), sport during leisure time (Questions 9-12), and PA during leisure excluding sport (Questions 13-16) [5]. We defined total index as total PA index, which were summed up of work, sport, and leisure-time index. The questionnaire defined three levels of occupational/work PA, namely low (e.g., clerical work, driving, shop keeping, teaching, studying, housework, medical practice and all other occupations with a university education), middle (e.g., farming, factory work, and carpentry), and high (e.g., dock work, construction work, and sport). Similarly, the questionnaire categorized sports into three levels: low (e.g., billiards, sailing, bowling and golf: average energy expenditure 0.76MJ/h), middle (e.g., badminton, cycling, dancing, swimming, and tennis: average energy expenditure 1.26MJ/h), and high (e.g., boxing, basketball, rugby, football, and rowing: average energy expenditure 1.76MJ/h). A sport score was calculated from a combination of the intensity of the sport which was played, the amount of time per week playing that sport, and the proportion of the year in which the sport was played regularly. Questions in each of the three indices (work, sport, and leisure) were scored on a five-point Likert scale, ranging from “1 = never” to “5 = always” or “5 = very often”. Summing the three indices gives a total PA index [11, 12]. We applied a five-point Likert scales to all of the three indices and only in sports index, we applied the combinations of intensity and duration.

A simple PA questionnaire

We measured PA by a simple questionnaire in 2009. The questionnaire has 4 options (“1” is spending most of time at home, “2” is working with almost sitting or less playing sports, “3” is working with a lot of movement and standing or playing active sports, and “4” is doing hard works), and subjects chose one of them.

Data collection

Medical history, smoking habits, and alcohol intake were ascertained by a questionnaire. Smoking and alcohol intakes were classified as current habitual use or not. Height and weight were measured, and body mass index (BMI) was calculated as an index of obesity. Waist circumference was measured at the level of umbilicus in the standing position. Blood pressure (BP) was measured in the supine position twice at 3-minute intervals using a standard sphygmomanometer. The second BP was taken after 5 deep breaths, and that was used for analysis.

Blood was drawn from the antecubital vein in the morning after a 12-hour fast for determinations of lipids profiles (total cholesterol, triglycerides, high-density [HDL], and low-density lipoprotein cholesterol [LDL]), fasting plasma glucose (FPG), HbA_{1c} (NGSP), insulin, serum urea nitrogen, creatinine, uric acid and serum HGF levels. Fasting blood samples were centrifuged within 1 hour after collection. Serum HGF levels was measured by the ELISA [14] and the other chemistries were measured at a commercially available laboratory (Kyodo Igaku Laboratory, Fukuoka, Japan). The estimate of insulin resistance by homeostasis model assessment (HOMA) score was calculated with the formula: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 as described by Matthews et al. [15]. Insulin resistance was defined as HOMA ≥ 1.73 according to the diagnostic criteria used in Japan [16]. Estimated glomerular filtration rate (eGFR) was calculated according to the following estimation formula that has been recommended by the Japan Society of Nephrology: eGFR (mL/min/1.73^2) = (194 × Scr $^{-1.094}$ × age $^{-0.287}$) × (0.739 for females) [17].

We divided into 2 groups (poor and good) by the median score of total PA index (median score was 7.75) in 1999, and also into 2 groups by a simple PA questionnaire in 2009. “Poor” was defined as subjects who chose “1” or “2”, and “good” was subjects who chose “3” or “4” of simple questionnaires. Using these 4 PA groups such as continuously low PA, increased PA, decreased PA, and continuously high PA, we compared their HGF levels in 10 years. We further investigated the development of hypertension, dyslipidemia, diabetes, and subjects who were suffering from CVD and cancer in 2009. The information was coded independently in accordance with the rules of the Seven Countries Study [9].

This study was approved by the Ukiha Branch of the Japan Medical Association, by the City Council of Tanushimaru, and by the Ethics Committee of Kurume University. All participants gave informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

Statistical analysis

Because of skewed distributions, natural logarithmic transformations were performed for HOMA index triglycerides and □-glutamyl transpeptidase (□-GTP). Log-transformed values were used for the statistical calculation and reconverted to antilogarithm forms in the tables. Gender, the medications for hypertension, dyslipidemia, and diabetes, smoking habits, and alcohol intake were used as dummy variables.

First, we performed univariate and multivariate regression analyses for correlates of physical activity in 1999 and 2009 in the cross-sectional study. Second, we compared serum HGF levels by the 4 PA groups in 1999 and 2009 using analysis of co-variance (ANCOVA) adjusted for age and sex. Third, we compared the risk of development of hypertension, dyslipidemia, diabetes, CVD, and cancer by 4 PA groups using ANCOVA adjusted for age and sex. Finally, in order to compare the prevalence of CVD by 4 PA groups, we performed a logistic regression analysis adjusted for age and sex. Statistical significance was defined as a p value less than 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Of 1,920 participants, we excluded 600 subjects from whom we were not able to evaluate PA and HGF levels. We also excluded 417 subjects who did not undergo health check-ups in 2009. The remaining 903 (341 males and 562 females: mean age of 59.6 years) subjects were finally included in this analysis, and the relationships among PA and the HGF levels were examined.

Cross-sectional study

Demographic data for the 903 participants in 1999 and 2009 are shown in **Table 1**. The data indicated that most people were nonobese, normotensive, normolipidemic, and nondiabetic. Ten years later, BMI and waist circumference became larger. Heart rate, systolic and diastolic BPs were significantly higher in 2009 than in 1999. TC, TG, HDL, uric acid, FPG, HbA_{1c}, HOMA index were also increased. The serum HGF levels were significantly higher in 2009 than in 1999. The uses of medications for hypertension, dyslipidemia, and diabetes were also increased. Frequency of alcohol intake was increased, whereas, frequency of smoking was decreased.

Activity measurements

The mean total PA index in 1999 was 7.83, with work index of 3.36, sport index of 1.97, and leisure-time index of 2.50. The total PA index showed a normal distribution with a peak score of 7-8 (**Figure 1A**). In 2009, 35% of the participants selected PA score 1 and 20% of them selected PA score 4 (**Figure 1B**). Total number divided by the 4 physical activity groups in 1999 and 2009 were shown in **Figure 1C**. Stable low was the most prevalent, and stable high was the second.

Correlation between activity and comorbidities

Univariate regression analysis for correlates of total PA index in 1999 was shown in **Supplementary Table 1**. There was a significant relationship between total PA index and age (p=0.034), male gender (p=0.032), heart rate (p=0.004; inversely), HGF (p=0.0004; inversely), and HOMA index (p=0.026; inversely). Subjects with diabetes and hypertension were not associated with total PA index. Univariate regression analysis for correlates of PA score in 2009 was shown in **Table 2**. There was a significant relationship between PA score and age (p<0.0001; inversely), male gender (p<0.0001), BMI (p=0.002), heart rate (p<0.0001; inversely), diastolic BP (p=0.002), HGF (p=0.0005; inversely), ALT (p=0.023), γ-GTP (p=0.011), eGFR (p<0.0001), HOMA index (p=0.040; inversely), smoking (p=0.011), alcohol intake (p<0.0001), medication for hypertension (p<0.0001; inversely), medication for dyslipidemia (p=0.001; inversely). Multivariate linear regression analysis for correlates of total PA index adjusted for demographics and lifestyle factors in 1999 was shown in **Supplementary Table 2**. In the final model, total PA index (p=0.0002) was inversely associated with HGF adjusted for age, sex, BMI, total cholesterol, systolic BP, HOMA index, and smoking. Multivariate linear regression analysis for correlates of PA score adjusted for demographics and lifestyle factors in 2009 was shown in **Table 3**. In the final model, there was a significant relationship between PA score and waist circumference (p=0.020; inversely), heart rate (p=0.0001; inversely), HGF (p=0.003;

inversely), γ-GTP (p=0.041), eGFR (p=0.001), uric acid (p=0.004; inversely), FPG (p=0.002), medication for hypertension (p=0.007; inversely), medication for dyslipidemia (p=0.008; inversely) adjusted for age, sex, BMI, total cholesterol, systolic BP, HOMA index, and smoking.

Prospective study

Figure 2A shows the serum HGF levels in 2009 divided by the 4 PA groups. The serum HGF levels of increased PA group were significantly lower than those of stable low PA group (p=0.038). The serum HGF levels of stable high PA group were significantly lower than those of decreased PA group (p=0.019) adjusted for age and sex (**Figure 2B**).

Figure 2C shows the development of CVD by the 4 physical activity groups. The prevalence of CVD development in increased PA group was significantly lower than that in stable low PA group (p=0.021). After adjustment for age and sex, the prevalence of CVD development in increased PA group was still significantly lower than that of stable low PA group (p=0.012) (**Figure 2D**). Logistic regression analysis for correlates of the development of CVD was shown in **Table 4**. The adjusted odds ratio for the development of CVD in increased PA group compared to stable low PA group was 0.29 (95% CI: 0.11–0.81).

Discussion

The present study demonstrated that improvement of PA levels was associated with the decrease of HGF levels and CVD development. Further, there have been previously no reports regarding the associations between serum HGF level and improvement of PA among 4 PA groups such as stable low PA, increased PA, decreased PA, and stable high PA. These results suggest that HGF levels may be a useful indicator to reach the enough improvement of PA.

It is interesting to note that HGF level in increased PA group was the lowest among the 4 PA groups (**Figures 2A and 2B**). These results suggest that low PA at baseline is not too late and that there may be enough time to decrease HGF levels. In addition, it was also expected that the prevalence of CVD development in increased PA group was significantly lower than that in stable low PA group (**Figures 2C and 2D**).

Recent epidemiological reports from ARIC (Atherosclerosis Risk in Communities) study [18] suggested that maintaining recommended activity levels was associated with the lowest heart failure (HF), whereas those with any decrease in PA category had an increased HF risk. The mechanisms how PA changes were associated with HF risk are not fully understood. Increased levels of PA are associated with improved metabolic profiles, including decreases in FPG and BMI and increases in HDL-cholesterol. Because serum HGF levels were strongly associated with the metabolic files [3], our study may provide a key clue.

Reports from the Multi-Ethnic Study of Atherosclerosis (MESA) [19] indicated that higher average PA levels and higher PA increases over an average of 10-year period were associated with a more eccentric-

type of left ventricular remodeling pattern. Recent epidemiological study [20] suggested that a positive association between several circulating vascular growth factors including HGF and cardiac remodeling was shown with the known biological effects of these pro- and anti-angiogenic factors on the myocardium and conduit arteries. Although the target diseases were not completely the same as ours, two clinical studies [21,22] have shown the significant relationship between HGF and left ventricular remodeling, which may be explained by the correlation between PA levels and circulating HGF.

Strengths And Limitations

This study has several strengths. We have measured PA and serum HGF levels twice in 1999 and 2009. We used a population-based sample with robust longitudinal follow-up of disease outcomes such as CVD. Many baseline characteristics including conventional coronary risk factors were used to examine a relationship with PA levels. This study also has several limitations. First, we used different questionnaires to assess the levels of PA. We measured PA by BPAQ in 1999, and by a simple PA questionnaire in 2009. Second, self-report PA questionnaires were used, thereby, increasing recall bias. Third, we do not have any data regarding the detailed educational and income levels. Finally, the present study was performed in a single Japanese population and our conclusions may not be generalizable to other populations with different lifestyles and genetic backgrounds.

In conclusion, the present study clearly demonstrated that improvement of PA levels was associated with reduced HGF levels and CVD development in a general Japanese population. Serum HGF levels may be a useful biomarker to detect the PA improvement in the clinical settings.

Declarations

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Authors' contributions

Akiko Sakaue was involved with data acquisition, performed the statistical analyses and interpretation, and drafted the manuscript. Hisashi Adachi and Yoshihiro Fukumoto designed and conceptualized the study, directed its implementation, were involved with data acquisition and critically the manuscript. Mika Enomoto, Ako Fukami, Yume Nohara, Nagisa Morikawa, Maki Yamamoto, Hiromi Satoh contributed to

data acquisition and critically the manuscript. All authors have reviewed the manuscript. All authors gave final approval of the version to be published and agreed to its submission.

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Tables

Table 1. Characteristics of the subjects at baseline (1999) and in 2009

Variables	1999	2009	*p*
Age (year)	59.6±9.1	69.7±9.1	<0.0001
Sex (%, males)	38.3	38.3	-
Body mass index (kg/m^2)	23.2±3.1	23.4±3.3	0.0096
Waist circumference (cm)	76.8±9.2	84.6±9.7	<0.0001
Systolic blood pressure (mmHg)	130.8±19.6	134.6±19.5	<0.0001
Diastolic blood pressure (mmHg)	78.9±11.4	81.0±11.2	<0.0001
Heart rate (bpm/min)	62.8±9.2	64.8±10.0	<0.0001
Hepatocyte growth factor (ng/ml)	0.22±0.08	0.29±0.09	<0.0001
Estimated GFR (ml/min/1.73m^2)	58.1±12.4	72.2±16.6	<0.0001
Uric acid (μmol/L)	291.5±83.3	309.3±83.3	<0.0001
Total cholesterol (mmol/L)	5.2±0.9	5.3±0.9	0.0008
HDL-cholesterol (mmol/L)	1.5±0.4	1.6±0.4	<0.0001
LDL-cholesterol (mmol/L)	3.2±0.8	3.2±0.8	0.1522
Triglycerides† (mmol/L) (mean (range))	1.1 (0.3-13.5)	1.2 (0.1-9.4)	0.0003
HbA_{1c} (%) (NGSP)	5.6±0.6	5.9±0.6	<0.0001
Fasting plasma glucose (mmol/L)	5.3±0.8	5.6±1.3	<0.0001
HOMA index† (mean (range)	1.1 (0.2-24.9)	1.4 (0.1-105.4)	<0.0001
Smoking (%, yes)	13.6	7.7	<0.0001
Alcohol intake (%, yes)	22.4	40.3	<0.0001
Medication for hypertension (%, yes)	15.4	47.5	<0.0001
Medication for dyslipidemia (%, yes)	4.6	42.3	<0.0001
Medication for diabetes (%, yes)	1.9	11.3	<0.0001
Total index (max score 15)	7.83±1.18	-	-
a. Work index (max score 5)	3.36±0.67	-	-
b. Sport index (max score 5)	1.97±0.57	-	-
c. Leisure-time index (max score 5)	2.50±0.73	-	-
Physical activity score n (%)			
1 (mean (range))	-	304 (34.7)	-
2 (mean (range))	-	152 (17.3)	-
3 (mean (range))	-	242 (27.6)	-
4 (mean (range))	-	179 (20.4)	-

Data are mean ± standard deviation, geometric mean, range, or percent.

Total index = Total physical activity index (a+b+c)

Abbreviations; GFR; glomerular filtration rate, HDL-C; High-density lipoprotein cholesterol, LDL-C; Low-density lipoprotein cholesterol, $HbA_{1c;}$ Glycosylated hemoglobin A_{1c}

HOMA; Homeostasis model assessment

These variables were represented in the original scale after analysis using log (natural) transformed values.

ıble 2. Univariate linear regression analysis for correlates of physical activity score in 2009

Variables	β	SE	*p*
Age	-0.038	0.004	<0.0001
Sex (males=0, females=1)	-0.489	0.079	<0.0001
Body mass index	0.036	0.012	0.002
Waist circumference	0.002	0.004	0.639
Systolic blood pressure	-0.001	0.002	0.801
Diastolic blood pressure	0.011	0.004	0.002
Heart rate	-0.020	0.004	<0.0001
Hepatocyte growth factor	-1.500	0.432	0.001
AST	0.001	0.004	0.988
ALT	0.001	0.003	0.023
γ-GTP†	0.158	0.062	0.011
Estimated GFR	0.014	0.002	<0.0001
Uric acid	0.008	0.028	0.766
Total cholesterol	0.001	0.001	0.754
HDL-cholesterol	-0.003	0.003	0.301
LDL-cholesterol	0.001	0.001	0.500
Triglycerides†	0.112	0.077	0.145
HbA_{1c}	0.102	0.060	0.089
Fasting plasma glucose	0.002	0.002	0.192
HOMA-index†	-0.084	0.041	0.040
Smoking	0.369	0.144	0.011
Alcohol intake	0.438	0.078	<0.0001
Medication for hypertension	-0.334	0.077	<0.0001
Medication for dyslipidemia	-0.263	0.079	0.001
Medication for diabetes	-0.050	0.123	0.685

Abbreviations; AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, γ-GTP; Gamma glutamyl transferase, GFR; glomerular filtration rate, HDL-C; High-density lipoprotein cholesterol, LDL-C; Low-density lipoprotein cholesterol, $HbA_{1c;}$ Glycosylated hemoglobin A_{1c}, HOMA; Homeostasis model assessment

These variables were represented in the original scale after analysis using log (natural) transformed values.

Table 3. Multivariate linear regression analysis for correlates of physical activity score in 2009

variables	Model 1 β (SE)	*p*	Model 2 β (SE)	*p*	Model 3 β (SE)	*p*
Body mass index	0.020 (0.011)	0.066	-	-	-	-
Waist circumference	0.001 (0.004)	0.940	-0.016(0.007)	0.014	-0.015(0.007)	0.020
Systolic blood pressure	0.001(0.002)	0.702	0.001(0.002)	0.965	-	-
Diastolic blood pressure	0.002(0.003)	0.634	0.001(0.003)	0.925	0.001(0.005)	0.945
Heart rate	-0.015(0.004)	<0.0001	-0.015(0.004)	<0.0001	-0.014(0.004)	0.0001
Hepatocyte growth factor	-1.177(0.413)	0.004	-1.257(0.414)	0.003	-1.242(0.422)	0.003
Estimated GFR	0.008(0.002)	0.002	0.008(0.002)	0.001	0.008(0.002)	0.001
Uric acid	-0.068(0.029)	0.017	-0.086(0.029)	0.004	-0.085(0.030)	0.004
AST	-0.002(0.003)	0.488	-0.002(0.003)	0.528	-0.002(0.003)	0.582
ALT	-0.002(0.003)	0.602	-0.002(0.003)	0.454	-0.002(0.003)	0.524
γ-GTP†	-0.121(0.064)	0.057	-0.142(0.064)	0.027	-0.134(0.065)	0.041
Total cholesterol	0.001(0.001)	0.666	-	-	-	-
HDL-cholesterol	-0.001(0.003)	0.714	0.001(0.003)	0.902	-0.001(0.003)	0.836
LDL-cholesterol	0.001(0.001)	0.442	0.001(0.002)	0.584	0.001(0.002)	0.620
Triglycerides†	0.025(0.072)	0.730	-0.030(0.077)	0.701	0.005(0.082)	0.952
HbA_{1c}	0.075(0.056)	0.177	0.062(0.056)	0.273	0.080(0.057)	0.165
Fasting plasma glucose	0.003(0.002)	0.033	0.003(0.002)	0.046	0.006(0.002)	0.002
HOMA-index†	-0.002(0.039)	0.969	-0.034(0.042)	0.414	-	-
Smoking	-0.164(0.144)	0.257	-0.150(0.144)	0.298	-	-
Alcohol intake	0.122(0.086)	0.157	0.117(0.086)	0.173	0.116(0.087)	0.187
Medication for hypertension	-0.166(0.075)	0.027	-0.196(0.076)	0.010	-0.222(0.082)	0.007
Medication for dyslipidemia	-0.186(0.075)	0.013	-0.220(0.077)	0.004	-0.206(0.077)	0.008
Medication for diabetes	-0.102(0.114)	0.369	-0.122(0.115)	0.286	-0.120(0.116)	0.303

Abbreviations; SE; Standard deviation, GFR; glomerular filtration rate,
AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, γ-GTP; Gamma glutamyl transferase,
HDL-C; High-density lipoprotein cholesterol, LDL-C; Low-density lipoprotein cholesterol,
$HbA_{1c;}$ Glycosylated hemoglobin A_{1c}, HOMA; Homeostasis model assessment
Model 1: adjusted for age and sex.
Model 2: adjusted for Model 1 + body mass index, total cholesterol, and systolic blood pressure.
Model 3: adjusted for Model 2 + HOMA index, and smoking.

Table 4. Odds ratios for the development of CVD during the period from 1999 to 2009 according to the subgroups defined by physical activity levels in 1999 and in 2009

	Number of			Adjusted for age and sex	
Physical activity levels	event/subjects	OR (95%CI)	p value	OR (95%CI)	p value
Stable low	23/248	1(reference)		1(reference)	
Increased	5/182	0.28(0.10-074)	0.0312	0.29(0.11-0.81)	0.0694
Decreased	17/197	0.92(0.48-1.78)	0.0717	0.73(0.37-1.44)	0.3223
Stable high	11/225	0.50(0.24-1.06)	0.5203	0.49(0.23-1.07)	0.5958

Abbreviations; CVD; Cerebro-cardiovascular disease, OR; Odds ratio

Figures

Figure 1A

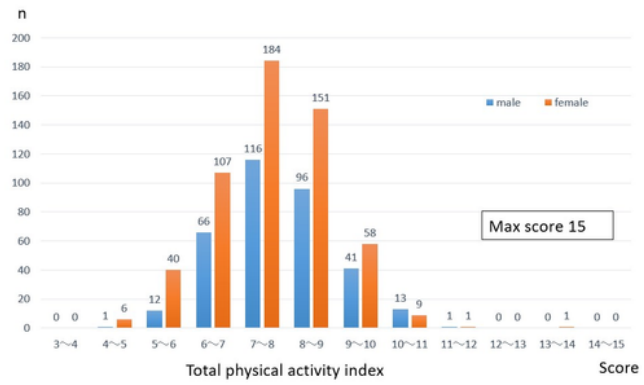


Figure 1B

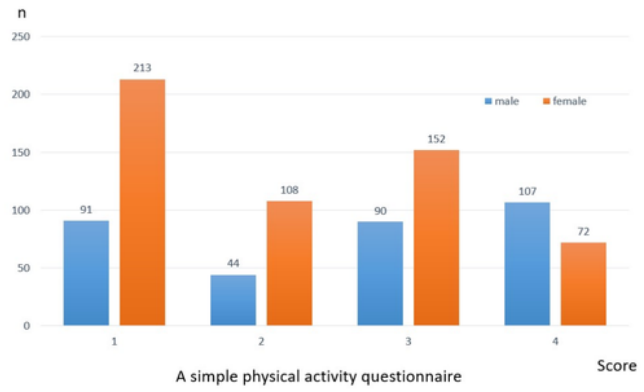
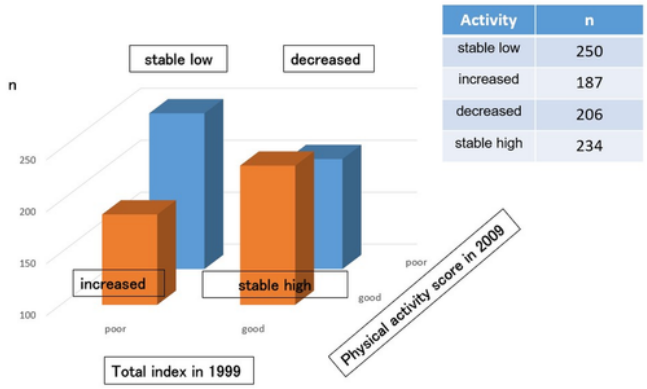


Figure 1C



Activity	n
stable low	250
increased	187
decreased	206
stable high	234

Figure 1

Distribution of PA levels. A: Distribution of the PA index (Total index, BPAQ) in 1999. B: Distribution of the simple PA questionnaire in 2009. C: Participants number divided by the 4 physical activity groups in 1999 and 2009.

Figure 2A

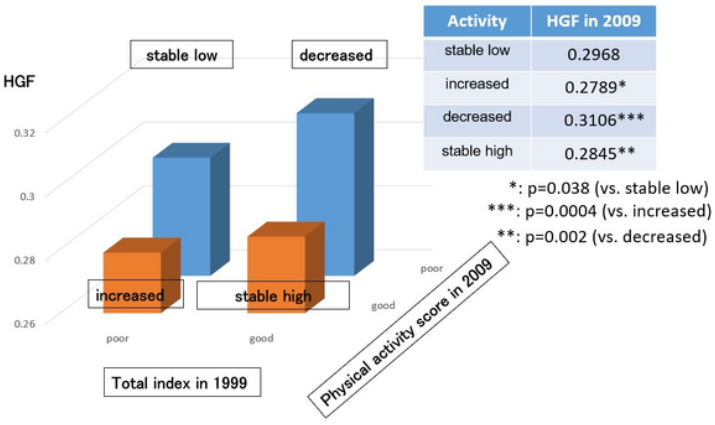


Figure 2B

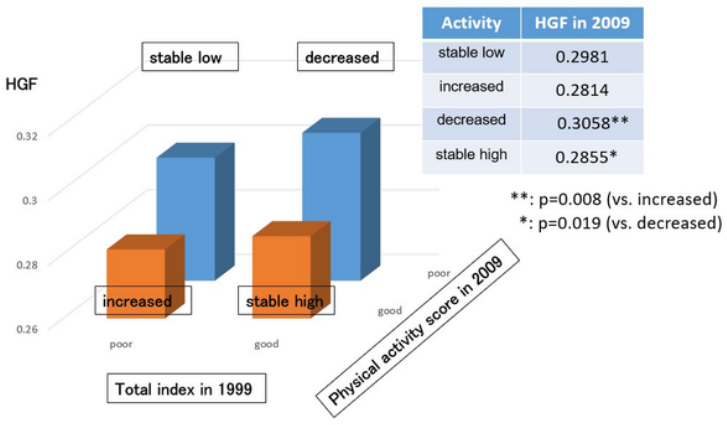


Figure 2C

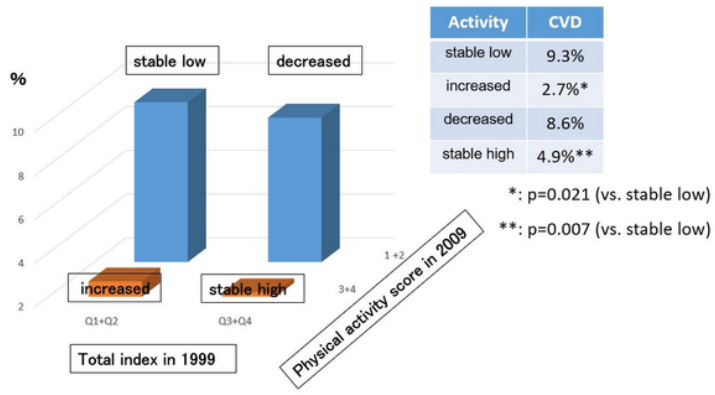


Figure 2D

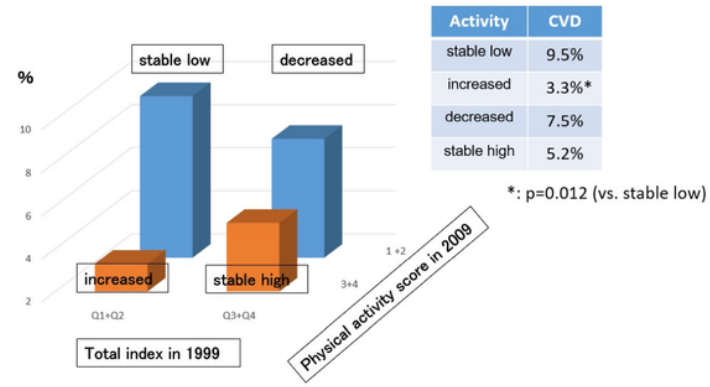


Figure 2

HGF levels and CVD development by the 4 physical activity groups in 1999 and 2009 A: Serum HGF levels by the 4 physical activity groups in 1999 and 2009. B: Serum HGF levels by the 4 physical activity groups in 1999 and 2009 adjusted for age and sex. C: CVD development by the 4 physical activity groups. D: CVD development by the 4 physical activity groups adjusted for age and sex.

Supplementary Files

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