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Inverse association between physical activity and blood glucose is independent of sex, menopause status and first-degree family history of diabetes

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ABSTRACT

Aims/Introduction: Exercise training is a recognized strategy central to the prevention, treatment, and management of diabetes and prediabetes. The aim of the present study was to investigate the association between physical activity and blood glucose, as well as the influence of sex, menopause status and family history of diabetes.

Materials and Methods: Participants with normal weight were selected from Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal Study, and divided into inactive (moderate-to-vigorous-intensity physical activity [MVPA] <30 min/week), low-degree (MVPA ≥30 and ≤420 min/week) and high-degree (MVPA >420 min/week) activity groups.

Results: A total of 2,601 individuals with an average age of 57.85 ± 8.39 years were enrolled. Multivariate ANOVA uncovered that after adjustment for sex and menopause status, and family history of diabetes, respectively, fasting plasma glucose, 2-h plasma glucose and glycated hemoglobin A1c decreased through inactive, low-degree and high-degree activity groups (all P for trend <0.05). The association of blood glucose indexes with physical activity was independent of this association with sex and menopause status, and first-degree family history of diabetes, respectively. Multivariate linear regression analyses showed that MVPA was an independent factor associated negatively with fasting plasma glucose, 2-h plasma glucose and glycated hemoglobin A1c, respectively (all $P < 0.01$).

Conclusions: A higher degree of physical activity was associated with lower blood glucose regardless of sex, menopause status and first-degree family history of diabetes. MVPA is a negative factor associated with blood glucose independently. Physical activity of adequate duration and intensity is strongly recommended to individuals with susceptibility to diabetes as a result of sex and family history, but without overweight/obesity.

INTRODUCTION

In China, the prevalence of diabetes has increased significantly and has reached epidemic proportions. The prevalence of diabetes has almost quadrupled from 1994 to 2007, and increased to 10.9% in 2013. Furthermore, the prevalence of prediabetes was 35.7%, indicating that >388 million of people in China had prediabetes[1,2]. Despite the rapid increase in incident diabetes and prediabetes, there has not been enough attention paid to prevention. Physical inactivity has been one of the major risk

factors for the development of type 2 diabetes mellitus[3–5]. Exercise training is a recognized strategy that is central to the prevention, treatment and management of diabetes and prediabetes[6–8].

Hyperglycemia develops in diabetes when the capacity of insulin secretion is exceeded by the metabolic demands. Therefore, sex differences in insulin sensitivity might contribute to the susceptibility of diabetes[9]. Women experience dramatic changes in hormones after menopause, which alters aspects of glucose homeostasis, such as glucose effectiveness[10]. In addition, first-degree relatives of patients with diabetes (FDR) show

insulin resistance and β-cell dysfunction before they develop diabetes[11]. It remains unclear whether the difference in glucose metabolism between men, premenopausal women and post-menopausal women, and between FDR and people without a family history of diabetes (non-FDR) would interfere with the effects of physical activity on glucose metabolism.

Notably, 48.1% of Chinese people with normal weight have prediabetes[1], and a sedentary lifestyle leads to adverse changes in body fat and further metabolic abnormalities in this population[12]. The association of physical activity with glucose metabolism, like other lifestyle interventions[13], might differ between normal weight and overweight/obese individuals. Given that most previous research focused on overweight/obese people, few studies have been carried out to investigate the association between physical activity and glucose metabolism in normal weight individuals[14]. The goal of the present study was to investigate the association between physical activity and blood glucose in a population with normal weight, and the influence of sex and menopause status, and family history of diabetes on this association.

METHODS

Study population
The present work was a part of the baseline survey from Risk Evaluation of Cancers in Chinese Diabetic Individuals: A Longitudinal Study (REACTION), carried out among 259,657 adults, who were aged ≥40 years in 25 communities across mainland China, between 2011 and 2012[15]. This study investigated the relationship of diabetes and cancer. A total of 4,918 participants from four communities of Wenzhou City were randomly screened and underwent examination at their community hospital separately. Participants with normal weight (body mass index ≥18.5 and <25) were enrolled. Other exclusion criteria were as follows: established cardiovascular and cerebrovascular diseases, severe liver or renal dysfunction, acute infection, tumors, and psychiatric disease. Based on these criteria, a total of 2,601 participants were included for the current analysis.

The present study was carried out in accordance with the Declaration of Helsinki and approved by the Ruijin Hospital Ethics Committee, Shanghai Jiao Tong University School of Medicine. All of the participants provided written informed consent before participation.

Questionnaire interview
A standardized questionnaire was used during the clinical visit to record information, including demographic characteristics, family history of diabetes and indicators for lifestyle, such as physical activity, total sitting time per week, and smoking and drinking status.

Physical activity level was evaluated according to the International Physical Activity Questionnaire with questions on the frequency and duration of moderate and vigorous activities, which were administered by self-administration with the last week of recalled physical activity[16]. Physically active was defined as moderate-to-vigorous-intensity physical activity (MVPA) ≥30 min per week, and physically inactive was defined as MVPA <30 min per week[17]. Based on their median value of MVPA (420 min/week), physically active participants were further divided into low-degree and high-degree groups.

First-degree relatives were defined as those having one or more FDR (parent, sibling or offspring) with diabetes[18].

Current smoking was defined as smoking at least one cigarette per day for >6 months[19]. Current drinking was defined as consuming one or more alcoholic drink on ≥1 day during the past 30 days[20]. Menopause was defined as at least 12 consecutive months of amenorrhea without other medical causes[21].

Physical examination
Each participant underwent a comprehensive physical examination with a standard protocol by trained physicians[22]. Examinations included measurement of anthropometric indexes (body height, weight, waist and hip circumferences) and blood pressure. Body mass index was calculated by weight (kg) divided by height squared (m[2]). Waist-to-hip ratio was determined as waist circumference divided by hip circumference. Blood pressure was assessed three times at 5-min intervals using a standard Omron intelligence electronic blood pressure monitor after participants had been comfortably seated for > 10 min. The average value of systolic blood pressure and diastolic blood pressure was calculated for the analysis.

Laboratory tests
Fasting plasma glucose (FPG), glycated hemoglobin A1c (HbA1c), total cholesterol, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol were detected after a fasting period of at least 8 h by using the auto-analyzer. Participants without diagnosed diabetes had taken 75 g glucose orally, and participants with diabetes underwent a 100-g carbohydrate test. A blood sample (5 mL) was collected at 2 h to assess the 2-h plasma glucose (2hPG). The methods were described previously[22].

Statistical analysis
SPSS, version 16.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses in the present study. Data are presented as the mean ± standard deviation or median with the interquartile range for continuous variables and numbers (percentages) for categorical variables. Comparison between the two groups was carried out by an unpaired Student's t-test, Mann–Whitney U-test and χ^2-test for continuous and categorical variables, respectively. Multivariate ANOVA was applied to explore the interaction on blood glucose between sex and menopause status, and physical activity, and between a first-degree family history of diabetes and physical activity. Linear stepwise regression analysis was carried out to evaluate the independent factors associated with blood glucose. All reported P-values were two-tailed, with <0.05 considered to be statistically significant.

RESULTS

Clinical characteristics of the study participants

A total of 2,601 individuals with an average age of 57.85 ± 8.39 years (range 40.01–80.23 years) were enrolled in the present study. Among them, participants with prediabetes accounted for 20.95% (545 participants), and those with diabetes accounted for 19.65% (511 participants). The average diabetic duration for those with diagnosed diabetes was 7.82 years. A total of 279 participants had received hypoglycemic treatments, accounting for 10.73% of the present study population. Participants were divided into an inactive group (1,912 participants) and active group (689 participants). Compared with the inactive group, the active group showed lower levels of waist circumference, systolic blood pressure, diastolic blood pressure, FPG, 2hPG, HbA1c and triglyceride (all $P < 0.05$), but a higher level of high-density lipoprotein cholesterol ($P = 0.003$). The inactive group and active group did not differ significantly in respect of other variables (all $P > 0.05$; Table 1).

Interaction on blood glucose between sex and menopause status, and physical activity

According to the median MVPA value (420 min/week) in the physically active population, this group was further divided into low-degree and high-degree activity groups. In the inactive, low-degree and high-degree activity groups, FPG, 2hPG and HbA1c did not differ significantly between postmenopausal women and men (all $P > 0.05$). In the inactive and low-degree activity group, all of the blood glucose indexes (FPG, 2hPG and HbA1c) were higher in postmenopausal women and men than those in premenopausal women (all $P < 0.01$). In the high-degree activity group, only HbA1c was higher in postmenopausal women and men than that in premenopausal women (both $P < 0.05$; Figure 1).

Multivariate ANOVA uncovered that after adjustment for sex and menopause status, FPG (P for trend = 0.019), 2hPG (P for trend <0.001) and HbA1c (P for trend = 0.020) decreased through the inactive group, low-degree activity group and high-degree activity group (Figure 2a–c). The association of blood glucose indexes with sex and menopause status, and this association with physical activity are independent of each other (Figure 2).

Interaction on blood glucose between family history of diabetes and physical activity

In the inactive group, FDR showed higher levels of FPG, 2hPG and HbA1c than non-FDR (all $P < 0.001$). In the low-degree activity group, levels of FPG ($P = 0.042$) and HbA1c ($P = 0.004$) were higher in FDR. Whereas in the high-degree activity group, there were no significant differences in all of the blood glucose indexes between FDR and non-FDR (all $P > 0.05$; Figure 3).

Multivariate ANOVA showed that in non-FDR and FDR, FPG (P for trend <0.001), 2hPG (P for trend <0.001) and HbA1c (P for trend = 0.007) differed significantly among the inactive

Table 1 | Characteristics of the study participants

Variable	Total $n = 2,601$	Inactive $n = 1,912$	Active $n = 689$
Age (years)	57.61 (51.91–63.78)	57.28 (51.53–63.75)	58.07 (53.17–63.83)
Sex (men/women)	693/1,908	492/1,420	201/488
BMI (kg/m²)	22.67 (21.36–23.82)	22.67 (21.35–23.83)	22.64 (21.42–23.74)
W (cm)	82.00 (77.50–87.00)	82.00 (78.00–87.50)	81.00 (77.00–85.15)**
WHR	0.88 (0.84–0.92)	0.88 (0.84–0.92)	0.88 (0.84–0.91)
SBP (mmHg)	129.00 (117.17–142.67)	130.00 (117.67–143.00)	127.67 (116.33–142.33)*
DBP (mmHg)	78.33 (71.33–85.00)	78.67 (71.33–85.33)	76.67 (70.67–84.33)*
FPG (mmol/L)	5.34 (5.00–5.90)	5.40 (5.00–6.00)	5.30 (5.00–5.80)**
2hPG (mmol/L)	6.90 (5.80–9.05)	7.00 (5.84–9.33)	6.60 (5.50–8.05)**
HbA1c (%)	5.7 (5.4–6.1)	5.7 (5.4–6.1)	5.7 (5.4–6.0)*
TC (mmol/L)	5.41 (4.76–6.11)	5.39 (4.75–6.11)	5.49 (4.82–6.13)
TG (mmol/L)	1.37 (0.98–2.00)	1.40 (0.99–2.03)	1.30 (0.98–1.87)*
LDL-c (mmol/L)	3.15 (2.59–3.72)	3.14 (2.59–3.72)	3.16 (2.61–3.70)
HDL-c (mmol/L)	1.41 (1.21–1.64)	1.40 (1.21–1.63)	1.46 (1.23–1.69)*
Sitting time (min/week)	1,680 (840–2,310)	1,680 (840–2,505)	1,680 (840–2,100)
FDR, n (%)	555 (21.33)	401 (20.97)	154 (22.35)
Current smoking, n (%)	277 (10.65)	220 (11.51)	57 (8.27)
Current drinking, n (%)	348 (13.38)	252 (13.18)	96 (13.93)

Data are the mean ± standard deviation, median (interquartile range), and n (%). *$P < 0.05$ versus inactive group. **$P < 0.001$ versus inactive group. 2hPG, 2-h plasma glucose; BMI, body mass index; DBP, diastolic blood pressure; FDR, first-degree relatives of patients with diabetes; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; W, waist circumference; WHR, waist-to-hip ratio.
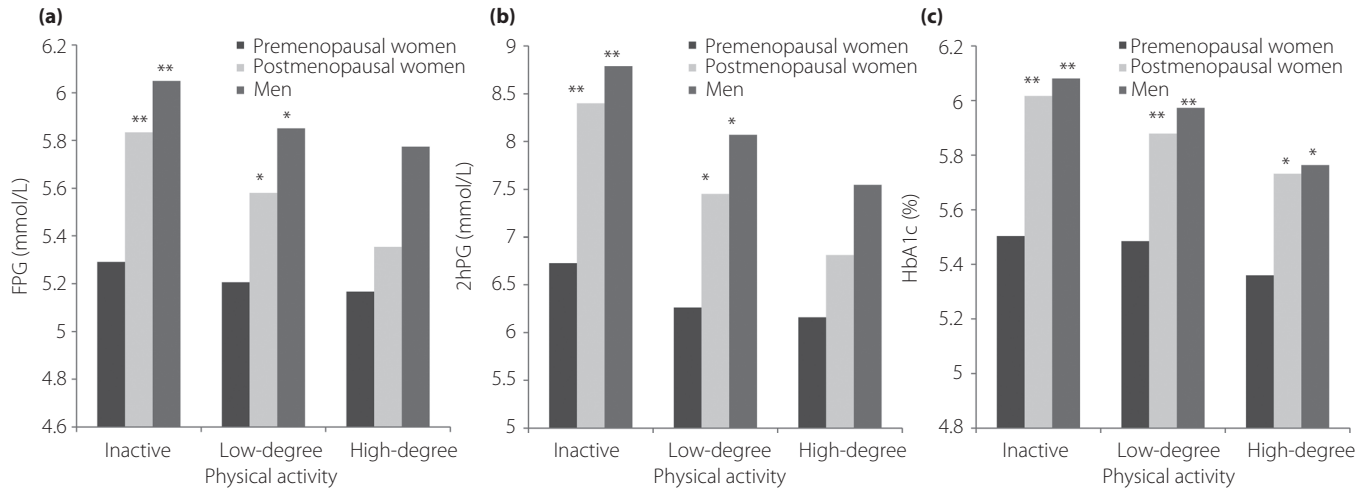
Figure 1 | Comparison of blood glucose between premenopausal women, postmenopausal women and men in different physical activity groups. (a) Comparison of fasting plasma glucose (FPG). (b) Comparison of 2-h plasma glucose (2hPG). (c) Comparison of glycated hemoglobin A1c (HbA1c). *$P < 0.05$ versus premenopausal women; **$P < 0.001$ versus premenopausal women.
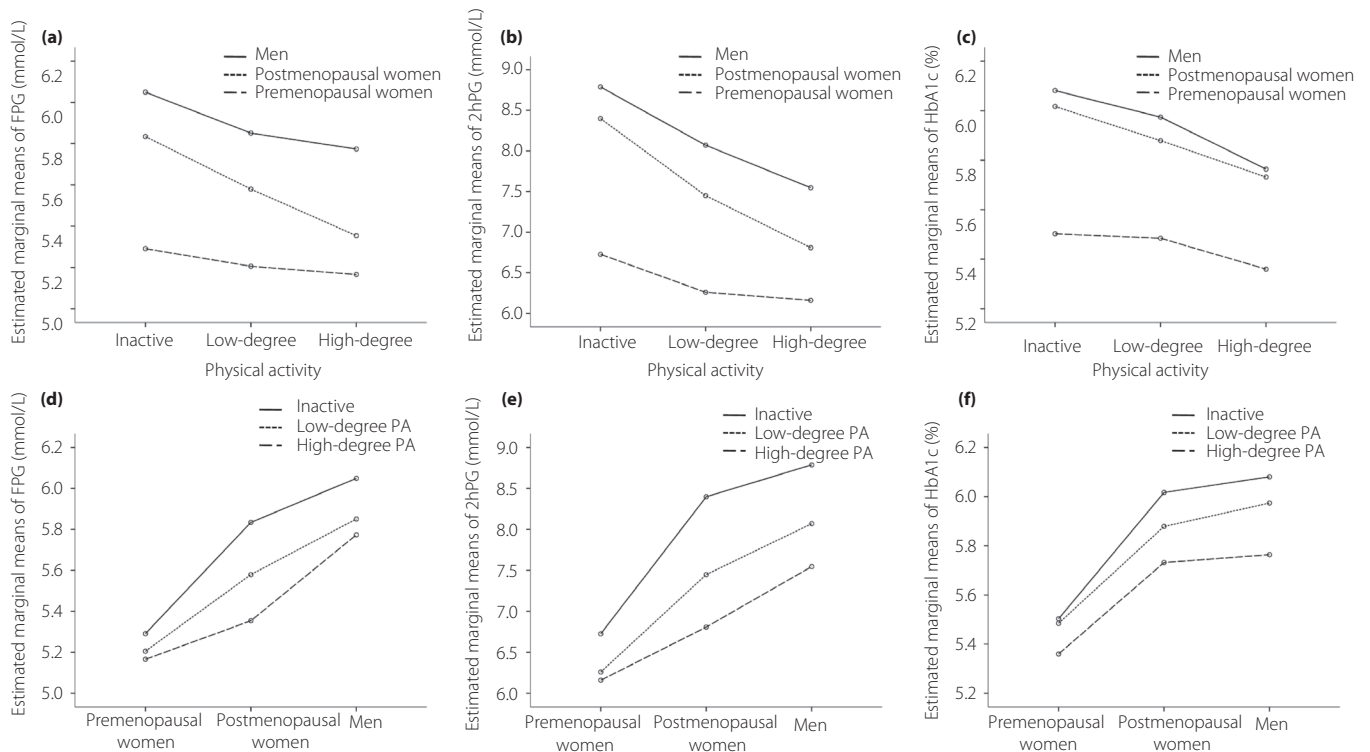

Figure 2 | Multivariate ANOVA of sex and menopause status, physical activity, and blood glucose. (a) Fasting plasma glucose (FPG) decreased through the inactive group, low-degree activity group and high-degree activity group (P for trend = 0.019); (b) 2-h plasma glucose (2hPG) decreased through the inactive group, low-degree activity group and high-degree activity group (P for trend < 0.001); (c) glycated hemoglobin A1c (HbA1c) decreased through the inactive group, low-degree activity group and high-degree activity group (P for trend = 0.020). (d) The association of FPG with physical activity is independent of sex and menopause status. (e) The association of 2hPG with physical activity is independent of sex and menopause status. (f) The association of HbA1c with physical activity is independent of sex and menopause status.
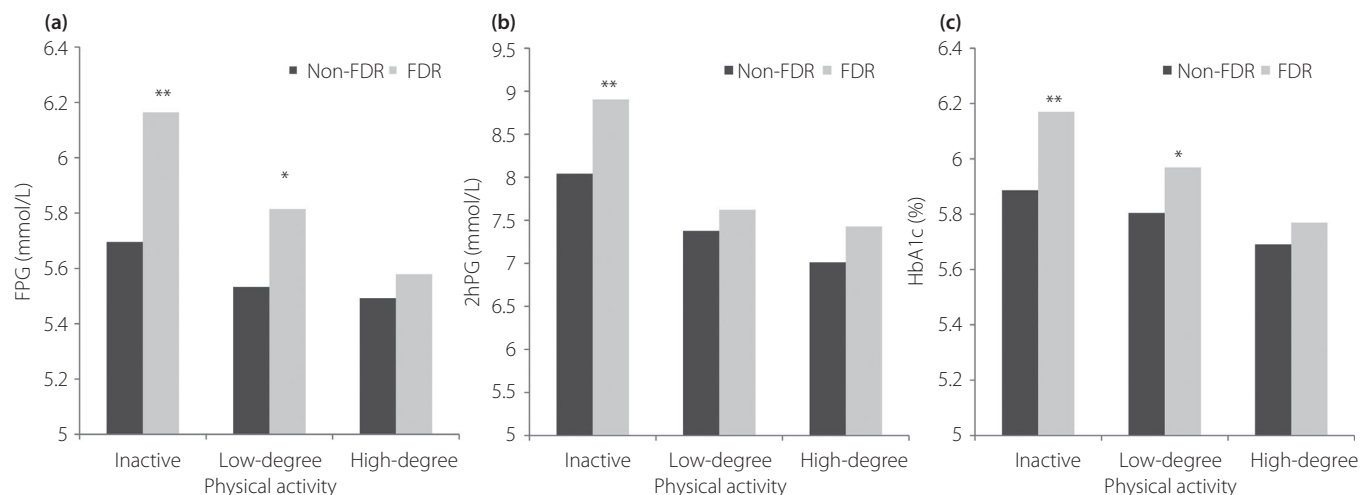
Figure 3 | Comparison of blood glucose between first-degree relatives of patients with diabetes (FDR) and non-FDR in different physical activity groups. (a) Comparison of fasting plasma glucose (FPG). (b) Comparison of 2-h plasma glucose (2hPG). (c) Comparison of glycated hemoglobin A1c (HbA1c). *$P < 0.05$ versus non-FDR; **$P < 0.001$ versus non-FDR.

group, low-degree activity group and high-degree activity group (Figure 4a–c), showing a decreasing trend with increasing degree of physical activity. The association of blood glucose indexes with family history of diabetes and this association with physical activity are independent of each other (Figure 4).

Multivariate linear regression analyses of blood glucose

Multivariate linear regression analyses defined age, sex and menopause status, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, FDR, current smoking, current drinking, sitting time, and MVPA as independent variables, and every blood glucose index as a dependent variable. The results showed that MVPA was an independent factor associated negatively with FPG (standardized $\beta = -0.057$, $P = 0.003$), 2hPG (standardized $\beta = -0.094$, $P < 0.001$) and HbA1c (standardized $\beta = -0.071$, $P < 0.001$), respectively (Table 2).

DISCUSSION

The present study showed that blood glucose indexes, including those reflecting the fasting and postload blood glucose, as well as long-term control of blood glucose, were lower in physically active population and further decreased with the increase in physical activity degree. In the high-degree activity population, there was no significant difference in the blood glucose between premenopausal women, postmenopausal women and men (except HbA1c), as well as FDR and non-FDR. Sex and menopausal status, and first-degree family history of diabetes did not interfere with the association between blood glucose and physical activity. MVPA stood out as an inverse and independent factor associated with the blood glucose.

Physical inactivity and obesity are critical and modifiable risk factors of diabetes. Different dimensions of physical activity are important for glucose metabolism in individuals with various characteristics of obesity[23]. Data from the 2014 Health Survey for England revealed that among adults with healthy weight, the prevalence of abnormal blood glucose showed a downtrend for the individuals with low-to-medium and further to high activity levels. Inactive individuals were more likely to have abnormal blood glucose levels than active individuals[17]. A study with 20 years of follow up of diabetes patients in Daqing, China, showed that physical activity intervention could reduce the incidence of diabetes by 43%, and the prevalence of diabetes was delayed by 3.6 years[7]. The early detection, screening and prevention of diabetes were almost exclusively carried out in overweight/obese populations[17]. However, a substantial proportion of individuals with normal weight have prediabetes[17], for whom dietary restriction and weight reduction, as typical measures to prevent prediabetes or type 2 diabetes mellitus, are not suitable[24,25].

In line with the previous studies, the present study found that among individuals with normal weight, blood glucose decreased with the expanded time of MVPA, suggesting that physical activity could serve as an alternative and efficient approach to prevent and improve diabetes, as well as its long-term management when the other lifestyle interventions are not working or suitable. Furthermore, MVPA was an independent protective factor of blood glucose. It was shown that physical activity might modulate type 2 diabetes mellitus, even in the absence of obesity, through a direct effect on insulin sensitivity, which was in agreement with the previous study[23].

Given the higher body fat percentage, women have similar insulin sensitivity to men for the whole body. Therefore, after
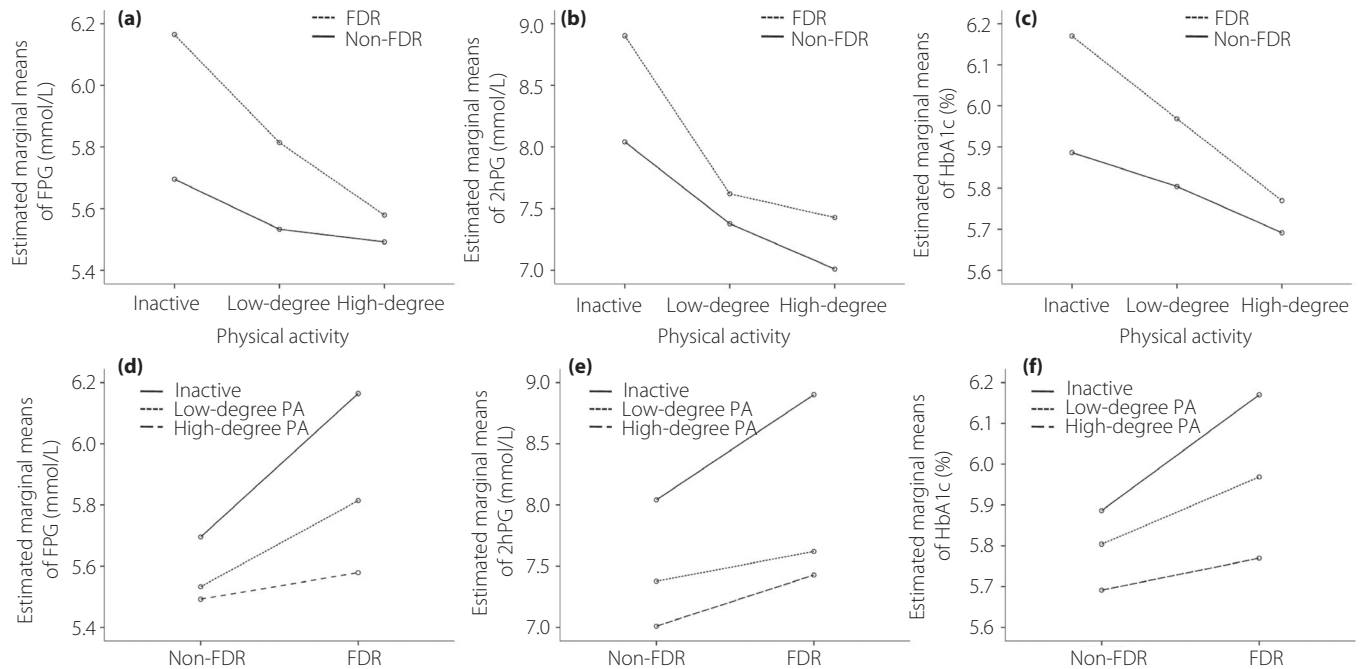
Figure 4 | Multivariate ANOVA of first-degree family history of diabetes (FDR), physical activity and blood glucose. (a) Fasting plasma glucose (FPG) decreased through the inactive group, low-degree activity group and high-degree activity group (P for trend <0.001). (b) The 2-h plasma glucose (2hPG) decreased through the inactive group, low-degree activity group and high-degree activity group (P for trend < 0.001). (c) Glycated hemoglobin A1c (HbA1c) decreased through the inactive group, low-degree activity group and high-degree activity group (P for trend = 0.007). (d) The association of FPG with physical activity is independent of FDR. (e) The association of 2hPG with physical activity is independent of FDR (f) The association of HbA1c with physical activity is independent of FDR.

Table 2 | Multivariate linear stepwise regression analysis

Independent variables	FPG			2hPG			HbA1c		
	Standardized β	t	P	Standardized β	t	P	Standardized β	t	P
Age	0.072	3.137	0.002	0.165	7.919	<0.001	0.138	5.992	<0.001
Sex and menopause status	0.074	3.455	0.001	–	–	–	0.065	3.058	0.002
W	0.051	2.518	0.012	0.094	4.901	<0.001	0.057	2.845	0.004
SBP	0.248	8.571	<0.001	0.304	10.867	<0.001	0.199	6.909	<0.001
DBP	−0.112	−4.110	<0.001	−0.139	−5.299	<0.001	−0.120	−4.420	<0.001
TG	0.105	5.100	<0.001	0.116	6.208	<0.001	0.112	5.485	<0.001
HDL-c	−0.049	−2.361	0.018	–	–	–	−0.045	−2.131	0.033
LDL-c	–	–	–	–	–	–	0.044	2.321	0.020
FDR	0.129	6.843	<0.001	0.101	5.522	<0.001	0.126	6.708	<0.001
PA time	−0.057	−3.022	0.003	−0.094	−5.162	<0.001	−0.071	−3.775	<0.001

Original independent variables included age, sex and menopause status, body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), first-degree relatives of patients with diabetes (FDR), current smoking, current drinking, sitting time, and physical activity duration. Sex and menopause status were defined as premenopausal women, postmenopausal women and men, given the value of 1, 2 and 3, respectively.

adjustment of body fat, women are more sensitive to insulin than men. Due to the differences in insulin sensitivity and fat distribution, men were more susceptible than women to the consequences of sedentary lifestyle and obesity[9]. For women,

the menopausal transition, characterized by a dramatic change in hormones and a subtler change in body fat distribution, is associated with increases in blood glucose levels and the incidence of diabetes[26]. Additionally, a first-degree family history of

diabetes predisposes individuals to developing this disease. FDR shows a 30–70% increase in risk of diabetes[18]. Both insulin resistance and β-cell dysfunction have been identified in FDR, even in the absence of diabetes[11].

The present study uncovered that with adequate duration and intensity of physical activity, the blood glucose of high-risk populations (postmenopausal women, men and FDR) would decrease to the levels close to the glucose levels of the low-risk population (premenopausal women and non-FDR). Although the environmental and genetic factors were varied, the decreasing trends of blood glucose across the inactive, low-degree activity and high-degree activity population were not changed. These findings suggested that physical activity is effective for improving the blood glucose regardless of sex and menopause status, and family history of diabetes, and this effect is supposed to be pronounced in high-risk populations.

There are several mechanisms underlying the association between physical activity and blood glucose. First, physical activity is capable of increasing energy consumption, reducing the onset of obesity, which is an independent risk factor for abnormal blood glucose[27]. Second, physical activity activates glucose transporter 4 to transfer to the surface of the muscle cells, leading to an increase in the uptake of skeletal muscle glucose and improvement of patients' insulin resistance[28]. Future study should be carried out to investigate the associations among diabetes, insulin resistance, central obesity, physical activity and muscle mass in individuals with healthy weight.

A major limitation of the present study was its nature of cross-sectional design, which made it infeasible to determine the causality between physical activity and blood glucose. In order to validate the association between physical activity levels and abnormal blood glucose in individuals with normal weight, a randomized controlled trial or a large cohort study should be carried out in the future. Another limitation was selection bias, as participants included in the study were limited to those who lived in the community and accepted medical examinations. Third, seasonal variations in physical activity participation might have influenced the collected data.

In conclusion, the present study showed that higher physical activity levels were associated with lower blood glucose in a population with normal weight, regardless of sex, menopause status and first-degree family history of diabetes. MVPA is a negative factor associated with blood glucose independently. Physical activity of adequate duration and intensity is strongly recommended to individuals with susceptibility to diabetes as a result of sex and family history, but without overweight/obesity.

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DISCLOSURE
The authors declare no conflict of interest.

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