TITLE: Physical activity and fasting glucose in adults with abnormal glucose metabolism: findings from two independent cross-sectional studies in China

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Abstract

Background. Relationship between physical activity and fasting glucose in people with abnormal glucose metabolism is not well-known. This study was to investigate dose-response association between physical activity (PAT) and fasting glucose from two independent surveys among Chinese adults with abnormal glucose metabolism.

Methods. 9419 adults with abnormal glucose metabolism from two independent surveys among Chinese adults were analyzed. Demographics, level of fasting glucose and PAT (in Met Score) were measured. Dose-response relationship between fasting glucose and PAT was assessed by natural cubic spline model. Certain threshold point was identified, and linear regression models were then used within each threshold interval to assess the liner relationship functions. Models were adjusted for confounding factors and were stratified in subgroup analyses by the main population characteristics including survey site, gender and age-group.

Results. Overall the relationship between PAT and fasting glucose was not in a linear association (Linearity test: $p<0.0001$). Level of fasting glucose was not associated with amount of PAT until a threshold point (square-rooted Met Score 66.6 (original Met score: 4,436 MET-minutes per week), 95% confidence intervals (65.2–69.3 (4,251-4,802 MET-minutes per week)). After this threshold, an inverse association was observed: each increase of every standard deviation of square-rooted Met Score 29.8 (888 MET-minutes per week) was associated with a 0.25 mmol/L decrease in fasting glucose, with adjustment for confounding factors. The patterns of relationship were tested to be consistent in subgroup analyses by survey site, gender and age group.

Conclusions. Our study indicated that among adults with abnormal glucose metabolism the level of fasting glucose was only inversely associated with square-rooted Met Score beyond a certain square-rooted Met Score amount.

Key words: Physical activity; glucose; metabolism disorder; Chinese; Cross-sectional

Introduction

Metabolism-related disease is associated with substantial health and economic burdens in human society, and the prevalence shows a continually increasing trend in both industrializing and industrialized countries [1]. Obesity is found as a significant risk factor [2], and many other potential risk factors have also been suggested in the emerging literature including physical inactivity [3, 4]. Both clinical and epidemiological studies have shown that adults with diabetes are associated with lower physical activity, compared with nondiabetic counterparts [5, 6]. Also, in adult populations some research has suggested that the physical activity is inversely associated with blood glucose level, independent of obesity [7]. However, findings on the association between physical activity and glucose in the general population has not yet been conclusive across the current literature which may be due to several aspects such as study design, study population and analytical method [8, 9]. In addition, the association between physical activity and fasting glucose level has not been fully investigated in metabolic syndrome (MS). The objective of the current study was to investigate the detailed relationship between amount of physical activity and level of fasting glucose among Chinese adults with abnormal glucose metabolism (MS or type 2 diabetes) in two large independent cross-sectional adult population databases.

Material and methods

Data Setting. Populations analyzed in this study were subsets, who fitted the inclusion criteria (see below Study Population), from two independent surveys. The Nanjing Community Cardiovascular Risk Survey, using random cluster sampling method [10], was carried out between 2011 and 2013 in the residents of 6 communities of urban areas in Nanjing, Jiangsu Province, China. In each community, one street district or township was randomly selected. All households (n=6445) in the selected street or town were included with only one participant aged ≥20 years selected from each household, without replacement. Overall, 5824 participants completed the survey question and following examination (response rate, 90%).

The Hefei Community Cardiovascular Risk Survey, also using random cluster sampling [11], was conducted between 2012 and 2013 in the residents of 10 rural areas in Hefei, Anhui Province, China. In each rural area, one township was randomly selected. All households (n=22,032) in the selected town were included with only 1 participant aged ≥20 years selected from each household, without replacement. Overall, 20,269 participants completed the survey and examination (response rate, 92%).

The Institutional Review Board of Jiangsu Province Hospital on Integration of Chinese and Western Medicine approved the Nanjing and Anhui surveys (ethical approval number 11-006). Signed written consents were obtained from all participants.

Study Population. The current research analyzed the population with abnormal glucose metabolism including those with type 2 diabetes and/or MS. Type 2 diabetes was defined using the WHO criteria for diabetes [12] or by self-reported previous diagnosis on type 2 diabetes, and MS was defined using the International Diabetes Federation criteria for MS [13].

Measures. Questionnaires and examinations in both surveys were completed, wherever possible, through face-to-face interviews by trained research staff. Questions included individual demographics (gender, age, body height and weight, waist circumference, smoking status), detailed physical activity measurements, and clinical information (self-reported diagnoses, medications and blood pressures).

Measurements including body height and weight, waist circumference, and blood pressure were taken three times using a standardized methodology on the same day in the local clinical center. Means of the two closest recordings were used. In both studies all staffs were received a training session on the use of a standardized protocol for anthropometric measurement techniques prior to study.

International Physical Activity Questionnaire (IPAQ) was used to obtain information on weekly job-, transport- and housework- related physical activities during recreational, sports and leisure time [14]. Participants were asked about the specific activities which they did for 10 minutes or longer during the past week by activity intensity, time duration per day and number of days per week. We summarized the data of amount of physical activity into metabolic equivalent task (MET)-minutes per week (Met Score). The square root of Met Score was used in analysis in the current study due to the data was left skewed.

An overnight-fasting venous blood specimen for measurement of serum glucose was collected by trained nurses using a vacuum tube containing sodium fluoride. The fasting time was verified prior to collecting the blood specimen. Individuals, who had not fasted for at least 10 hours, did not have their blood drawn. Fasting blood specimens collected in both surveys were processed at one examination center based in Nanjing. Plasma glucose and other blood measures such as levels of creatinine and lipid were measured by an automated analyzer according to manufacturer's instructions (Olympus AU600 auto analyzer (Olympus Optical, Tokyo, Japan)).

Statistical Analysis. Continuous variables were reported by median along with interquartile range (IQR). Categorical variables were reported as number with percentage. Dose-response relationship between the transformed (square-rooted) Met Score [x] and the level of fasting glucose was examined by natural cubic spline model [t]. The final threshold was defined as the cut-off point with a significant break in the regression coefficients and achieving the minimum AIC [15]. A 1000-bootstrapping was applied to estimate the 95% confidence interval (95% CI) of the final threshold [16]. The linear regression models were then used to quantify the linear relationships between the level of fasting glucose and amount of physical activity in data fragments separated by the identified threshold, with adjustment for confounding factors. In the sensitivity analyses, these models were repeated in each survey, gender, and age group (age<50 years, and age≥50 years). All analyses were processed by STATA 16.0 with statistical significance defined by a two-tailed p value less than 0.05.

Results

Population Characteristics. 9419 (36% of the total survey participants) were identified as having metabolic disorders (1873 in Nanjing survey, and 7546 in Hefei survey). Their demographic, clinical (including fasting glucose level) and physical activity information are presented in Table 1. Fasting glucose levels were 5.7 (IQR 5.1 to 6.6), 5.5 (4.9 to 6.5), and 5.5 (5.0 to 6.5) for Nanjing, Hefei and the pooled population, respectively. Amounts of physical activity (in square-rooted Met Score

/ original Met score) were 42.2 (IQR 28.1 to 64.3) / 1,781 (790-4,134) MET-minutes per week, 51.5 (35.5 to 71.5) / 2,652 (1,260-5,112) MET-minutes per week, and 50.0 (33.6 to 70.1) / 2,500 (1,129-4,914) MET-minutes per week, for Nanjing, Hefei and the combined population, respectively.

Physical Activity and Fasting Glucose. The dose-response relationship between of square-rooted Met Score and fasting glucose level after adjustment for confounding factors (including age, gender, survey site, blood pressures, body mass index, waist circumference, lipid profiles, creatinine, C-reaction protein, anti-hypertension treatment, anti-diabetes treatment, and lipid-lowering treatment) is demonstrated in Figure 1. A non-linear relationship was identified (Linearity test: $P<0.0001$): the level of fasting glucose remained stable before it decreased with the increase of square-rooted Met Score beyond a certain amount of physical activity threshold. The threshold (square-rooted Met score / original Met score) was found to be at 66.6 (95% CI: 65.2 to 69.3) / 4,436 (4,251 to 4,802) MET-minutes per week. Consistent findings for this dose-response relationship with the same threshold were observed in subgroup analyses by survey site, gender, or age group (Figure 1).

Table 2 shows the relationship of amount of physical activity with level of fasting glucose below and above the identified threshold. Below the threshold, no significant association was seen, whereas above the threshold increase of each standard deviation of square-rooted Met Score 29.8 (888 MET-minutes per week) was significantly associated with a 0.25 mmol/L decrease in fasting glucose in the pooled population, after adjustment for confounding factors. Similar association patterns were seen in subgroup analyses by survey site, gender, or age group

(Table 2).

Discussion

Physical activity has been consistently reported as having a positive impact on decreasing diabetes risk [17-20]. However, the findings on the association of physical activity with fasting glucose has not been conclusive. In the general population of young adults, the effect of physical activity on reduction of glucose level was strong and was shown to be increased with the increasing frequency, duration and intensity of exercise [21]. In middle aged healthy populations, one study found there was significant association in females but not in males [10, 22], while another study, which only recruited female samples for intervention, demonstrated no significant effect of physical activity on fasting glucose level [23]. Recent meta-analysis of randomized trials demonstrated that moderate increases in physical activity were associated with significant reduction in fasting glucose in both healthy and diabetic populations. However, the changes of fasting glucose were larger among diabetic patients [6]. Our study, which analyzed in adults with abnormal glucose metabolism, was generally in line with the previous literature. However, it demonstrated a more complex relationship between the amount of physical activity and level of fasting glucose: there was no association within a certain amount of activity; however, beyond the certain threshold the amount of physical activity was inversely associated with the level of fasting glucose.

Our study was novel in terms of the use of natural cubic spline models for the non-liner relationship. It contained more details in comparison to liner function models with which most previous research applied. Based on the information from our analysis, physical activity with moderate-to-vigorous intensity, sufficient duration and frequency is encouraged to reach the threshold with regard to blood glucose control.

This study benefits from its large sample size over 9000 individuals. However, it is limited by its cross-sectional design, therefore no formal attempt with regard to causality will be inferred. Data from questionnaire, as self-reported records, can be biased in many reasons, such as recall and response bias. However, thanks to the high response rates in both surveys such systematic error was not likely to be large. There may be potential bias between the two surveys, such as equipment, assay kit and research staff, on the measurement of fasting glucose level. However, the patterns of relationship between amount of physical activity and level of fasting glucose in each survey were highly consistent in subgroup analysis by survey site. In the pooled dataset, the association results were further adjusted for survey site in order to remove any such bias. Levels of fasting glucose are influenced by many factors including diseases, medications and lifestyle variables. Although in our surveys several potential confounding factors were collected and adjusted in statistical models, more and detailed data on morbidity, use of medication and lifestyle information were not available, which is a limitation of the current study. Our results were consistent in both surveys, however, populations were residents from the communities in eastern part of China, highlighting the need to investigate other populations to validate the generalizability of findings. Finally, as all analyses were preformed based on square-rooted scores, the significant difference of original scores with its relevant clinical difference could not be justified directly in the current study. Further replication studies in the external population are warranted.

Conclusion

In conclusion, our study using natural cubic spline models, showed that the non-linear relationship between physical activity and fasting glucose level exists in Chinese adults with abnormal glucose metabolism as fasting glucose fasting glucose was only inversely associated with square-rooted Met Score beyond a certain square-rooted Met Score amount. Future studies with prospective data are warranted to test whether blood glucose could be reduced through physical activity only when exercise and sports attaining to a certain threshold.

Author statement

All authors approved the final version of the manuscript to be published. All authors agreed to be accountable for all aspects of the work in ensuring the questions related to the accuracy or integrity of any part of the work. CLL takes final responsibility for the paper.

Conflict of interest

No potential conflicts of interest exist.

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None.

Ethical statement

The Institutional Review Board of Jiangsu Province Hospital on Integration of Chinese and Western Medicine approved the Nanjing and Anhui surveys (ethical approval number 11-006). Signed written consents were obtained from all participants.

Author contribution statement

DY, YC, LL: Conceived and designed the experiments, analyzed and interpreted the data, wrote the paper; YC, TC: Analyzed and interpreted the data, wrote the paper; YH, HM: conceived and designed the experiments, wrote the paper; All authors read and approved the final manuscript.

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Table 1. Characteristics of participants with metabolic disorder

	Pooled data	Nanjing	Hefei
N	9,419	1,873	7,546
Female gender	6,924 (73.5)	1,430 (76.4)	5,494 (72.8)
Age, years	54 (46 to 60)	54 (48 to 60)	54 (46 to 60)
Current smoker	1,439 (15.5)	281 (15.7)	1,158 (15.4)
Waist circumference, cm	88.2 (83.3 to 95.3)	87.3 (83.0 to 94.0)	88.4 (83.4 to 95.7)
Body mass index, kg/m^2	26.6 (24.5 to 28.8)	26.5 (24.5 to 28.6)	26.6 (24.5 to 28.8)
Systolic blood pressure, mmHg	139 (127 to 155)	137 (125 to 152)	140 (127 to 156)
Diastolic blood pressure, mmHg	86 (79 to 95)	85 (78 to 93)	87 (79 to 95)
Fasting glucose, mmol/L	5.5 (5.0 to 6.5)	5.7 (5.1 to 6.6)	5.5 (4.9 to 6.5)
Total cholesterol, mmol/L	4.7 (4.2 to 5.4)	4.6 (4.0 to 5.2)	4.8 (4.2 to 5.4)
Triglyceride, mmol/L	1.6 (1.1 to 2.3)	1.5 (1.0 to 2.3)	1.6 (1.1 to 2.3)
Low-density lipoprotein cholesterol, mmol/L	2.6 (2.2 to 3.1)	2.5 (2.1 to 2.9)	2.7 (2.2 to 3.2)
High-density lipoprotein cholesterol, mmol/L	1.3 (1.1 to 1.5)	1.3 (1.1 to 1.5)	1.3 (1.1 to 1.6)
Creatinine, mmol/L	86 (76 to 96)	86 (77 to 96)	86 (76 to 96)
C-reaction protein, mmol/L	1.2 (0.6 to 2.6)	0.6 (0.4 to 2.1)	1.2 (0.6 to 2.7)
Taking anti-hypertension agent, n (%)	2,302 (24.5)	441 (23.7)	1,861 (24.7)
Taking anti-diabetes agent or insulin, n (%)	842 (9.0)	134 (7.2)	708 (9.4)
Taking lowering lipid agent, n (%)	279 (3.0)	52 (2.8)	265 (3.5)
Square-rooted Met Score / original Met Score, MET-minutes per week	50.0 (33.6 to 70.1) / *2,500 (1,129 to 4,914)*	42.2 (28.1 to 64.3) / *1,781 (790 to 4,134)*	51.5 (35.5 to 71.5) / *2,652 (1,260 to 5,112)*

Continuous variables are presented by median (interquartile range), and categorical variables by number (percentage)

Table 2. Change of fasting glucose related to physical activity

Main and subgroup analyses	Change of fasting glucose per standard deviation of square-rooted Met Score	
	Below the threshold	Above the threshold
Main (pooled data)[¶]	0.09 (-0.01 to 0.20)	-0.25 (-0.35 to -0.14)
Nanjing survey[†]	0.09 (-0.03 to 0.23)	-0.18 (-0.32 to -0.04)
Hefei survey[†]	0.11 (-0.01 to 0.23)	-0.31 (-0.43 to -0.19)
Female[§]	0.07 (-0.002 to 0.14)	-0.24 (-0.35 to -0.13)
Male[§]	0.13 (-0.12 to 0.37)	-0.42 (-0.67 to -0.16)
Age<50 years[‡]	0.09 (-0.28 to 0.46)	-0.16 (-0.27 to -0.05)
Age≥50 years[‡]	0.02 (-0.09 to 0.12)	-0.28 (-0.44 to -0.12)

[¶]Adjusted for survey site, age, gender, blood pressures, body mass index, waist circumference, lipid profiles, creatinine, C-reaction protein, anti-hypertension treatment, anti-diabetes treatment, and lipid-lowering treatment;
[†]Adjusted for age, gender, blood pressures, body mass index, waist circumference, lipid profiles, creatinine, C-reaction protein, anti-hypertension treatment, anti-diabetes treatment, and lipid-lowering treatment;
[§]Adjusted for survey site, age, blood pressures, body mass index, waist circumference, lipid profiles, creatinine, C-reaction protein, anti-hypertension treatment, anti-diabetes treatment, and lipid-lowering treatment;
[‡]Adjusted for survey site, gender, blood pressures, body mass index, waist circumference, lipid profiles, creatinine, C-reaction protein, anti-hypertension treatment, anti-diabetes treatment, and lipid-lowering treatment;
One standard deviation of square-rooted Met Score is 29.8 (888 MET-minutes per week).
The threshold for square-rooted Met Score is 66.6 (4,436 MET-minutes per week).

Figure 1. Adjusted dose-dependent relationship between physical activity and fasting glucose among Chinese adults with metabolic disorder

In plot-(a): survey site, age, gender, blood pressures, body mass index, waist circumference, lipid profiles, creatinine, C-reaction protein, anti-hypertension treatment, anti-diabetes treatment, and lipid-lowering treatment were adjusted;
In plot-(b) & (c): age, gender, blood pressures, body mass index, waist circumference, lipid profiles, creatinine, C-reaction protein, anti-hypertension treatment, anti-diabetes treatment, and lipid-lowering treatment were adjusted;
In plot-(d) & (e): survey site, age, blood pressures, body mass index, waist circumference, lipid profiles, creatinine, C-reaction protein, anti-hypertension treatment, anti-diabetes treatment, and lipid-lowering treatment were adjusted;
In plot-(f) & (g): survey site, gender, blood pressures, body mass index, waist circumference, lipid profiles, creatinine, C-reaction protein, anti-hypertension treatment, anti-diabetes treatment, and lipid-lowering treatment were adjusted;