ORIGINAL RESEARCH PAPER

Physical activity as a determinant of fasting and 2-hour post-challenge glucose: a prospective cohort analysis of the NAVIGATOR trial

Running head: Physical activity as a determinant of fasting and 2-h glucose

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What's new?

- This is the first study to investigate the prospective relationship of daily step count, as measured by a pedometer, with fasting and 2-hour post-challenge glucose in an international clinical trial.
- Recent history of physical activity was weakly related to 2-hour glucose in those with a high risk of type 2 diabetes after taking into account the trajectory of 2-hour glucose established in the preceding 3 years.
- A 100% increase in daily step count was associated with a 0.9% reduction in 2-hour post-challenge glucose. There was no association for fasting glucose.

ABSTRACT

Aims: To investigate whether previous physical activity levels are associated with blood glucose levels in individuals with impaired glucose tolerance in the context of an international pharmaceutical trial.

Methods: Data were analysed from the NAVIGATOR trial, involving 9306 individuals with impaired glucose tolerance and high cardiovascular risk from 40 different countries, recruited 2002–2004. Fasting glucose, 2-hour post-challenge glucose, and physical activity (pedometer) were assessed annually. A longitudinal regression analysis was used to determine whether physical activity levels 2 years ($\mathbf{t}_{-2}$) and 1 year ($\mathbf{t}_{-1}$) previously were associated with levels of glucose, after adjusting for previous glucose levels and other patient characteristics. Those with four consecutive annual measures of glucose and two consecutive measures of physical activity were included.

Results: The analysis included 3964 individuals. Change in physical activity from $\mathbf{t}_{-2}$ to $\mathbf{t}_{-1}$ and activity levels at $\mathbf{t}_{-2}$ were both associated with 2-hour glucose levels after adjustment for previous glucose levels and baseline characteristics. However, associations were weak: a 100% increase in physical activity was associated with a 0.9% reduction in 2-hour glucose levels. In addition, previous physical activity only explained an additional 0.05% of the variance in 2-hour glucose over the variance explained by the history of 2-hour glucose alone (R^2=0.3473 vs. 0.3468). There was no association with fasting glucose.

Conclusions: In the context of a large international clinical trial, prior physical activity levels did not meaningfully influence glucose levels in those with a high risk of chronic disease, after taking into account participants' previous trajectory of glucose control.

INTRODUCTION

There is wealth of observational, experimental, and interventional evidence supporting the use of physical activity in the prevention and management of Type 2 diabetes [1-8]. For example, diabetes prevention programmes that have focused on physical activity, or incorporated physical activity promotion as part of a healthy lifestyle programme, have been effective at reducing the risk of Type 2 diabetes by up to 60%, and exercise training has been shown to improve glycaemic control in Type 2 diabetes, even in the absence of weight loss [5-7]. Consequently, physical activity forms a key facet of diabetes prevention and management programmes.

Although physical activity has proven a powerful therapeutic agent in promoting improved glycaemic control there is greater uncertainty about whether the accurate measurement of physical activity, or monitoring change in physical activity over time, should be included as important descriptive and covariate variables in clinical trials that are focused on interventions other than those related to lifestyle, such as pharmaceutical products. Clinical trials invest substantial resources in ensuring that participants are intensively phenotyped with clinical and behavioural characteristics, such as levels of adiposity and smoking status that are known to be predictive of future cardiometabolic health, and the degree to which the investigated intervention may change these factors over time. However, the ~~vast~~ majority of clinical trials have ~~fail~~ not ~~to~~ measured and/or reported levels of physical activity. Whilst we have recently shown that physical activity and change in physical activity act as determinants of cardiovascular disease in the context of an international clinical trial [9], the importance of physical activity in relation to other commonly defined primary end points, such as glucose levels, has not been adequately elucidated.

The international NAVIGATOR trial [10-12]uniquely employed multiple annual measures of fasting glucose, 2-hour post-challenge glucose (2-h glucose), and pedometer-assessed physical activity. We used these data to quantify the degree to which previous physical activity levels were associated with fasting and 2-h glucose, after taking into account the

historical trend in glucose levels established over preceding years in addition to common clinical characteristics. We hypothesised that previous levels of physical activity were associated with 2-h glucose.

METHODS

Study Design and Population

We analysed data from the NAVIGATOR trial, described in detail elsewhere [10-12]. In brief, NAVIGATOR was a multicentre, randomised, placebo-controlled, 2 × 2 factorial trial designed to investigate whether nateglinide (meglitinide analogue) and/or valsartan (angiotensin II receptor antagonist) reduced the risk of Type 2 diabetes and cardiovascular events in those with established risk factors for these outcomes. Those with impaired glucose tolerance (IGT) and existing cardiovascular disease (if age 50 years or older) or those with IGT and at least one additional cardiovascular risk factor (if age 55 years or older) were included in the study. IGT was confirmed in included individuals with an oral glucose tolerance test and defined as a 2-h glucose value of at least 140 mg/dL (7.8 mmol/L) and less than 200 mg/dL (11.1 mmol/L); in addition, inclusion criteria required fasting glucose in the range of 95 mg/dL (5.3 mmol/L) to less than 126 mg/dL (7.0 mmol/L). Exclusion criteria included evidence of hepatic disease, evidence of renal failure, history of malignancy within the last 5 years, use of oral antidiabetic agents or insulin within the last 5 years, or a concomitant condition that could interfere with efficacy and safety data. Further details of the inclusion and exclusion criteria are listed elsewhere [10]. Participants were recruited from 806 centres in 40 different countries. In total, 42,149 patients were screened for inclusion. Of these, 32,843 patients were subsequently excluded, predominantly for failure to meet protocol-defined IGT criteria, leaving 9306 fully eligible subjects who were enrolled in the study between January 2002 and January 2004 and randomised [1:1:1:1] to 1 of the 4 treatment combinations. Participants were followed for an average of 6 years.

Clinical Characteristics

All individuals underwent an oral glucose tolerance test at baseline and annually using standardised criteria according to the American Diabetes Association Guidance, 1997 [13]. Lipid profile, renal function, blood and pulse pressure, electrocardiogram, body weight, and height were also assessed. In addition, a detailed medical history was collected, including previous cardiovascular disease, other concomitant diseases/conditions, and smoking status. All outcomes were assessed using the same standard operating procedures across sites.

Physical Activity

Habitual ambulatory activity was objectively assessed by research-grade pedometers (Accusplit, San Jose, CA, USA), dispatched to all study centres. Two weeks after the initial baseline clinical measurements were taken, participants were fitted with a pedometer and instructed to wear it during waking hours for 7 consecutive days. Participants were given a log book and instructed to write down their daily step count at the end of each day. Ambulatory activity levels were re-assessed annually using the same criteria. For the purposes of this study, those reporting zero steps per day and those reporting more than 40,000 steps per day were removed from the analysis. Those with at least 1 day of valid data were included. The vast majority of activity logs included in this analysis (93%) displayed 7 days of data, with 98% having at least 5 days.

Lifestyle Modification

All participants were referred to a study-specific lifestyle modification programme that was designed to help achieve and maintain a 5% weight loss, reduce the amount of saturated and total dietary fat intake, and increase physical activity levels to 150 minutes weekly. Personnel within each site were trained to administer the programme at each clinic visit within the first 12 months (at 0.5, 1, 3, 6, and 12 months).

Statistical Analysis and Data Inclusion

Habitual physical activity levels were measured as the average number of steps taken per day (total summed pedometer counts divided by the number of days that data were captured).

NAVIGATOR included annual measures of physical activity, fasting glucose, and 2-h glucose; therefore, we sought to incorporate all available data in order to maximise statistical power and ensure a robust design. To this end, we undertook a longitudinal regression analysis according to the linear model

$$\boldsymbol{Y_{i,t0} = \beta_0 + \beta_1 \times Y_{i,t-1} + \beta_2 \times Y_{i,t-2} + \beta_3 \times Y_{i,t-3} +}$$

$$\boldsymbol{\beta_4 \times \Delta X_{i,(t-2)\rightarrow(t-1)} + \beta_5 \times X_{i,t-2} + \underline{\beta_p^{Tr}} \times \underline{C_i} + e_{i,t}}$$

where $\boldsymbol{Y_{i,t0}}$ is the log-transformed glucose level for individual $\boldsymbol{i}$ at time $\mathbf{t}_0$, and similarly defined for prior times $\mathbf{t}_{-1}$ (minus 1 year), $\mathbf{t}_{-2}$ (minus 2 years), and $\mathbf{t}_{-3}$ (minus 3 years), and $\boldsymbol{e_{i,t}}$ is a mean zero normally distributed error. We let $\boldsymbol{\Delta X_{i,(t-2)\rightarrow(t-1)}}$ be the change in log-transformed activity from time $\mathbf{t}_{-2}$ to $\mathbf{t}_{-1}$; $\boldsymbol{X_{i,t-2}}$ is log-transformed activity at time $\mathbf{t}_{-2}$, and $\underline{\boldsymbol{C_i}}$ denotes a vector of baseline covariates for the $\boldsymbol{i}^{\text{th}}$ individual. The superscript *Tr* denotes a vector transpose where $\boldsymbol{\beta_p}$ is a vector of parameters associated with baseline covariates in the model. Thus, the estimate of $\boldsymbol{\beta_4}$ describes the association between previous change in $\boldsymbol{X}$ (pedometer counts) measured between $\mathbf{t}_{-2}$ and $\mathbf{t}_{-1}$ and a subsequent change in the response $\boldsymbol{Y}$ (glucose level), after conditioning on the prior history of $\boldsymbol{Y}$ in the previous 3 years. $\boldsymbol{\beta_4}$ and $\boldsymbol{\beta_5}$ together describe the relationship between the history of $\boldsymbol{X}$ and subsequent $\boldsymbol{Y}$ after accounting for the prior history of $\boldsymbol{Y}$.

Given the inclusion of lagged values of glucose as independent variables, the evaluation of glucose as the response variable started at year 3 and continued to year 6. Only participants with glucose values at time $\mathbf{t}_0$, preceded by 3 annual glucose values at $\mathbf{t}_{-1}$, $\mathbf{t}_{-2}$, $\mathbf{t}_{-3}$, and a pedometer value at $\mathbf{t}_{-1}$ and $\mathbf{t}_{-2}$, were included in the analysis. More lags were not considered because the number of patients contributing consecutive data points became small. However, responses at year 4, 5, and 6 were analysed as repeated measures wherever available; therefore, some participants contributed more than one set of responses to the analysis. Generalized estimating equations with a robust standard error estimate were used to account for correlation from using multiple responses within individuals. For those diagnosed with Type 2 diabetes during the study, data were censored when diabetes medication was initiated. Glucose values were

natural-log-transformed in order to meet assumptions for normality; pedometer-determined physical activity levels were also natural-log-transformed for linearity. The linear modelling assumption of homoscedastic variance was assessed, and no violation was detected.

The analysis was conducted before and after adjustment for the following baseline characteristics previously identified as factors associated with the development of type 2 diabetes and cardiovascular disease within the Navigator cohort [14, 15]: randomisation group, age, sex, race, region, smoking status, waist circumference, systolic blood pressure, pulse pressure, chronic obstructive pulmonary disease, atrial fibrillation/flutter, low-density and high-density lipoprotein cholesterol, platelets, haemoglobin, log of albumin/creatinine ratio, sodium, estimated glomerular filtration rate, electrocardiogram abnormalities, congestive heart failure, cerebrovascular disease, coronary heart disease, pulmonary disease, peripheral artery disease, and family history of diabetes. An interaction term was fitted for randomisation group in order to investigate whether the results were modified by treatment allocation. Missing covariate data (variables other than glucose or physical activity data) at baseline were imputed; less than 3% of data were missing per covariate included in the model. A single imputed dataset using Markov Chain Monte Carlo and regression methods was used. Descriptive data are presented as medians [interquartile ranges (IQRs)], and regression results are presented as effect estimates (95% confidence intervals).

To account for the fact that some participants had a low number of days that contributed to the average pedometer data at a given time point, thus potentially weakening the degree of alignment with true habitual activity levels [16], analyses were repeated when only those with at least 5 days of valid pedometer data at each time point were included. We also investigated whether results were modified when those with peripheral artery disease were removed from the analysis.

RESULTS

In total, 3964 (43%) participants had at least one required sequence of pedometer data with fasting or 2-h glucose data and were included in the analysis (participants' required 4 consecutive annual glucose measures at $\mathbf{t}_0$, $\mathbf{t}_{-1}$, $\mathbf{t}_{-2}$, and $\mathbf{t}_{-3}$ with consecutive annual pedometer data at $\mathbf{t}_{-1}$ and $\mathbf{t}_{-2}$); the vast majority of included participants (>95%) contributed more than one set of responses to the analysis. In total, there were 9202 responses for 2-h glucose and 9621 responses for fasting glucose. Table 1 provides the characteristics of the included study participants. Compared with those who were excluded, those who were included had similar levels of fasting glucose and 2-h glucose. However, those who were included were more active (median 6501 [IQR 4235-9323] steps/day vs. 5294 [3375-8038]), more likely to come from Asia (9.7% vs. 3.1%), less likely to be white (79.3% vs. 85.9%), and had a lower BMI (29.0 [26.3-32.6] kg/m^2 vs. 30.1 [27.2-33.9] kg/m^2) (see supplementary Table 1).

Table 2 details the results of the analysis for 2-h glucose. Participants' history of change in physical activity between $\mathbf{t}_{-2}$ (2 years previously) and $\mathbf{t}_{-1}$ (1 year previously) was associated with 2-h glucose levels at time $\mathbf{t}_0$, after adjustment for the history of 2-h glucose levels in the preceding 3 years and clinical characteristics at baseline. However, associations were relatively weak; on conversion of the logarithmic scale, a 100% increase in physical activity levels from $\mathbf{t}_{-2}$ to $\mathbf{t}_{-1}$ was associated with a 0.9% reduction in 2-h glucose levels. In contrast, previous glucose values at $\mathbf{t}_{-1}$, $\mathbf{t}_{-2}$, and $\mathbf{t}_{-3}$ were all strongly, and independently, associated with 2-h glucose at time $\mathbf{t_0}$. When physical activity was excluded from the model, 34.68% of the variance in 2-h glucose levels at time $\mathbf{t}_0$ were explained by the history of 2-h glucose at $\mathbf{t}_{-1}$, $\mathbf{t}_{-2}$, and $\mathbf{t}_{-3}$ (R^2=0.3468). Adding physical activity levels at $\mathbf{t}_{-2}$ and $\mathbf{t}_{-1}$ to the model explained 34.73% of the variance (R^2=0.3473), suggesting that the inclusion of the recent history of physical activity only helped explain an additional 0.05% of the variance in 2-h glucose levels. No associations between physical activity and fasting glucose were seen (Table 3). However, as with 2-h glucose, previous measures of fasting glucose were strongly associated with fasting glucose at time $\mathbf{t}_0$.

There was a significant interaction for change in physical activity with treatment allocation (p= 0.042) for associations with 2-h glucose, with associations strongest in the

placebo group compared to those receiving valsartan ± nateglinide (see supplementary Table 2). Nonetheless, the results remained weak. In the placebo group, a 100% increase in physical activity was associated with a 2.3% reduction in 2-h glucose. There was no interaction by treatment allocation for associations with fasting glucose. Analyses were unaffected when those with less than 5 days of valid pedometer data at each time point (n=297) or those with peripheral artery disease (n=100) were excluded.

DISCUSSION

Prior levels of physical activity were associated with 2-h glucose control after adjusting for multiple confounding variables, including the trajectory of 2-h glucose levels in the preceding 3 years. However, associations were weak, such that in the cohort overall a 100% increase in physical activity levels was associated with a 0.9% reduction in 2-h glucose levels. Results were modified by treatment allocation with the strongest associations seen in the placebo group; however, a 100% change in physical activity was still only associated with a 2.3% reduction in 2-h glucose in this group. Therefore, this study suggests that, on average, glucose levels are not meaningfully influenced by previous levels of physical activity in those who have a history of IGT and high cardiovascular disease risk, and that any effect is dwarfed by the trajectory in glucose levels already established over previous years.

Although physical activity has been strongly associated with the risk of Type 2 diabetes and glucose levels previously [1-3], to our knowledge this is the first epidemiological investigation to quantify the extent to which previous physical activity levels act as a determinant of fasting and 2-h glucose levels independently to the trajectory in health status already established. Previous epidemiological evidence underpinning the long-term association between physical activity and metabolic health has been based on observational research that employed crude self-reported measures of physical activity and lacked temporal depth beyond 2 time points. These limitations introduce considerable uncertainty into the evidence. Self-reported levels of habitual physical activity have low validity, particularly for assessing total

levels of habitual physical activity across all contexts (i.e., home, leisure, transport, etc.) [17], and are influenced by factors beyond total physical activity volume, such as memory, social desirability, and the amount of volitional versus incidental physical activity undertaken. Furthermore, limiting observational analysis to 1 or 2 time points negates the ability to assess whether physical activity or change in physical activity can reverse the trajectory in glucose levels that has already been established in preceding years. The importance of this was confirmed by the present study in which previous glucose levels were strong determinants of current glucose levels for both fasting and 2-h measures. Therefore, without adjustment for this historical trajectory, previous studies have been unable to adequately address the possibility of reverse causation.

Strengths of the study include the multiple annual measures of fasting glucose, 2-h glucose, and physical activity allowing complex longitudinal analysis to be undertaken, the large cohort, pedometer-assessed physical activity, and that participants were rigorously characterised. In addition, the sample comprised a large international population with IGT and at high cardiovascular risk, making the results broadly generalisable to diabetes and cardiovascular disease prevention programmes globally. The primary limitation is the large amount of missing data, which may act to limit generalisability. In particular, those who were included in the analysis were significantly more active at baseline compared to those who were excluded; therefore, these results may not be representative of ~~highly~~ inactive adults with IGT. Other limitations include open pedometer use, in which participants self-recorded their daily steps in a diary, and the fact that wear-time and intensity of movement were not assessed; these factors could act to increase variation and reduce validity. Despite the complex modelling used, this remains an observational investigation and precludes direct inferences of causality. Furthermore, many of the mechanisms linking physical activity to 2-h glucose levels act acutely [18], which was not taken into account by the study design. However, this study specifically focused on elucidating the value of previous physical activity as a determinant of fasting glucose and 2-h glucose in those with a high risk of Type 2 diabetes and cardiovascular disease. It was

not designed, and consequently cannot be used, to provide insight into the therapeutic potential of physical activity in promoting improved glucose control in high-risk individuals.

In conclusion, in the context of a large international clinical trial, prior physical activity levels are not meaningfully associated with fasting or 2-h glucose levels in those with a high risk of Type 2 diabetes and cardiovascular disease, after taking into account the trajectory in glucose control already established.

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Table 1. Baseline characteristics of patients included in the analysis

Characteristic	N	Value
Age, years	3964	63 (58-68)
Sex (female)	3964	1996 (50.4%)
Region	3964	
Asia		384 (9.7%)
Europe		2018 (50.9%)
Latin America		716 (18.1%)
North America		704 (17.8%)
Other		142 (3.6%)
Race	3964	
White		3145 (79.3%)
Black		59 (1.5%)
Asian		404 (10.2%)
Other		356 (9.0%)
Current smoker	3964	363 (9.2%)
Clinical History		
Congestive heart failure	3964	137 (3.5%)
Coronary heart disease*	3964	1113 (28.1%)
Cerebrovascular disease‡	3964	322 (8.1%)
Pulmonary disease∫	3964	35 (0.9%)
Peripheral artery disease**	3964	100 (2.5%)
Chronic obstructive pulmonary disease	3964	164 (4.1%)
Family history of diabetes	3964	1446 (36.5%)
Clinical Features		
BMI, kg/m^2	3963	29.0 (26.3-32.6)
Systolic blood pressure, mmHg	3960	140 (128-150)
Diastolic blood pressure, mmHg	3960	82 (77-90)
Pulse pressure, mmHg	3960	56 (48-65)
Atrial fibrillation or flutter	3964	131 (3.3%)
Laboratory Variables		
Fasting glucose, mmol/L	3961	6.1 (5.7-6.4)
2-hr glucose, mmol/L	3962	9.0 (8.4-9.9)
Total cholesterol, mmol/L	3953	5.36 (4.69-6.09)
HDL cholesterol, mmol/L	3895	1.24 (1.03-1.47)
LDL cholesterol, mmol/L	3778	3.23 (2.61-3.88)
Triglycerides, mmol/L	3951	1.69 (1.21-2.36)
Haemoglobin, g/L	3890	146 (138-155)
eGFR, $mL/min/1.73m^2$	3952	80.3 (68.8-91.7)
Urine albumin/creatinine ratio, mg/mmol	3869	0.76 (0.50-1.53)
Sodium, mmol/L	3951	143 (141-144)

Characteristic	N	Value
Medications		
ACE inhibitor	3962	238 (6.0%)
Alpha blocker	3962	136 (3.4%)
Beta blocker	3962	1551 (39.1%)
Calcium channel blocker	3962	1246 (31.4%)
Diuretic	3962	1158 (29.2%)
Lipid-lowering agent	3962	1459 (36.8%)
Antihypertensives	3962	2792 (70.5%)
Aspirin	3962	1355 (34.2%)
Electrocardiogram		
Normal	3904	1914 (49.0%)
Clinically insignificant abnormality	3904	136 (35.0%)
Clinically significant abnormality	3904	624/3904 (16.0%)
Pedometer		
Baseline pedometer count (steps/day)	3465	6501 (4235-9323)

Continuous variables are presented as median (25^{th}-75^{th} percentiles) and categorical variables as number (%).
*Myocardial infarction, angina, positive stress test, or coronary revascularisation.
‡Stroke, transient ischemic attack.
∫Pulmonary embolism or deep venous thrombosis.
**Limb or foot amputation, intermittent claudication, limb arterial bypass procedure.
Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Associations of previous physical activity and change in physical activity with 2-hour glucose levels

	Log 2-hr glucose	
Model 1	**Effect Estimate (95% CI)**	**P value**
Change in log physical activity $\mathbf{t}_{-2}$ to $\mathbf{t}_{-1}$	-0.013 (-0.024, -0.003)	0.015
Log physical activity $\mathbf{t}_{-2}$	-0.008 (-0.016, -0.001)	0.037
Log 2-hr glucose, mmol/L, $\mathbf{t}_{-1}$	0.378 (0.353, 0.403)	<0.001
Log 2-hr glucose, mmol/L, $\mathbf{t}_{-2}$	0.262 (0.237, 0.287)	<0.001
Log 2-hr glucose, mmol/L, $\mathbf{t}_{-3}$	0.150 (0.125, 0.176)	<0.001
Model 2		
Change in log physical activity $\mathbf{t}_{-2}$ to $\mathbf{t}_{-1}$	-0.013 (-0.024, -0.002)	0.018
Log physical activity $\mathbf{t}_{-2}$	-0.010 (-0.018, -0.001)	0.029
Log 2-hr glucose, mmol/L, $\mathbf{t}_{-1}$	0.373 (0.347, 0.398)	<0.001
Log 2-hr glucose, mmol/L, $\mathbf{t}_{-2}$	0.258 (0.233, 0.283)	<0.001
Log 2-hr glucose, mmol/L, $\mathbf{t}_{-3}$	0.150 (0.124, 0.175)	<0.001

$\mathbf{t}_{-1}$, $\mathbf{t}_{-2}$, and $\mathbf{t}_{-3}$ are used to denote measurements taken at 1 year, 2 years, and 3 years before the dependent variable was assessed.

Model 1: All variables shown in the tables were entered into the same model and therefore adjusted for each other. No other adjustments were carried out.

Model 2: As per Model 1, plus adjustment for the following baseline clinical characteristics: age, sex, race, region, smoking status, waist circumference, systolic blood pressure, pulse pressure, family history of diabetes, COPD, atrial fibrillation/flutter, LDL and HDL cholesterol, platelets, haemoglobin, log of albumin/creatinine ratio, sodium, eGFR, ECG abnormalities, congestive heart failure, cerebrovascular disease, coronary heart disease, pulmonary disease, peripheral artery disease and randomised treatment.

Table 3. Associations of previous physical activity and change in physical activity with fasting glucose levels

	Log fasting glucose	
Model 1	**Effect Estimate (95% CI)**	**P value**
Change in log pedometer, $\mathbf{t}_{-2}$ to $\mathbf{t}_{-1}$	-0.001 (-0.006, 0.004)	0.596
Log pedometer count, $\mathbf{t}_{-2}$	-0.001 (-0.005, 0.003)	0.571
Log fasting glucose, mmol/L, $\mathbf{t}_{-1}$	0.400 (0.364, 0.436)	<0.001
Log fasting glucose, mmol/L, $\mathbf{t}_{-2}$	0.232 (0.198, 0.267)	<0.001
Log fasting glucose, mmol/L, $\mathbf{t}_{-3}$	0.211 (0.178, 0.243)	<0.001
Model 2		
Change in log pedometer, $\mathbf{t}_{-2}$ to $\mathbf{t}_{-1}$	-0.002 (-0.007, 0.003)	0.441
Log pedometer count, $\mathbf{t}_{-2}$	-0.002 (-0.006, 0.002)	0.321
Log fasting glucose, mmol/L, $\mathbf{t}_{-1}$	0.393 (0.357, 0.429)	<0.001
Log fasting glucose, mmol/L, $\mathbf{t}_{-2}$	0.230 (0.196, 0.265)	<0.001
Log fasting glucose, mmol/L, $\mathbf{t}_{-3}$	0.206 (0.173, 0.239)	<0.001

$\mathbf{t}_{-1}$, $\mathbf{t}_{-2}$, and $\mathbf{t}_{-3}$ are used to denote measurements taken at 1 year, 2 years and 3 years before the dependent variable was assessed.

Model 1: All variables shown in the tables were entered into the same model and therefore adjusted for each other. No other adjustments were carried out.

Model 2: As per Model 1, plus adjustment for the following baseline clinical characteristics: age, sex, race, region, smoking status, waist circumference, systolic blood pressure, pulse pressure, family history of diabetes, COPD, atrial fibrillation/flutter, LDL and HDL cholesterol, platelets, haemoglobin, log of albumin/creatinine ratio, sodium, eGFR, ECG abnormalities, congestive heart failure, cerebrovascular disease, coronary heart disease, pulmonary disease, peripheral artery disease and randomised treatment