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Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin within the general population: a cross-sectional analysis of Health Survey for England

Authors: Kishan Bakrania* [1, 2, 3, 4], Thomas Yates* [2, 3], Charlotte L. Edwardson [2, 3], Danielle H. Bodicoat [2, 4], Dale W. Esliger [3, 5], Jason M.R. Gill [6], Aadil Kazi [2, 3], Latha Velayudhan [7, 8], Alan J. Sinclair [9], Naveed Sattar [6], Stuart J.H. Biddle [10], Mark Hamer [3, 5], Melanie J. Davies [2, 3] and Kamlesh Khunti [2, 4]

* = joint first authors

[1] Department of Health Sciences, University of Leicester, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[2] Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[3] National Institute for Health Research (NIHR) Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit (BRU), Diabetes Research Centre, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[4] National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care – East Midlands (CLAHRC – EM), Diabetes Research Centre, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[5] School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, Leicestershire, LE11 3TU, United Kingdom.

[6] British Heart Foundation Glasgow Cardiovascular Research Centre (BHF GCRC), Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, G12 8TA, United Kingdom.

[7] Psychiatry for the Elderly, Department of Health Sciences, University of Leicester, Leicester, Leicestershire, LE1 7RH, United Kingdom.

[8] Older People's Mental Health, Oxleas National Health Service (NHS) Foundation Trust, Bridgeways, Bromley, BR8 2JA, United Kingdom.

[9] Diabetes Frail Ltd, Aston University, Birmingham, West Midlands, B4 7ET, United Kingdom.

[10] Institute of Sport, Exercise & Active Living, Victoria University, Melbourne, VIC 8001, Australia.

Corresponding author: Dr. Charlotte L. Edwardson, Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, Leicestershire, LE5 4PW, United Kingdom. Phone: +44(0)116 258 8577. Email: ce95@le.ac.uk.

Author email addresses: Kishan Bakrania (kb318@le.ac.uk), Thomas Yates (ty20@le.ac.uk), Charlotte L. Edwardson (ce95@le.ac.uk), Danielle H. Bodicoat (dhm6@le.ac.uk), Dale W. Esliger (D.Esliger@lboro.ac.uk), Jason M.R. Gill (Jason.Gill@glasgow.ac.uk), Aadil Kazi (Aadil.Kazi@uhl-tr.nhs.uk), Latha Velayudhan (lv24@le.ac.uk), Alan J. Sinclair (sinclair.5@btinternet.com), Naveed Sattar (Naveed.Sattar@glasgow.ac.uk), Stuart J.H. Biddle

(Stuart.Biddle@vu.edu.au), Mark Hamer (M.Hamer@lboro.ac.uk), Melanie J. Davies (melanie.davies@uhl-tr.nhs.uk) and Kamlesh Khunti (kk22@le.ac.uk).

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ABSTRACT

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Objectives: To investigate the independent and combined associations of objectively measured moderate-to-vigorous-intensity physical activity (MVPA) and body mass index (BMI) with glycated haemoglobin (HbA1c) in a nationally representative sample of English adults.

Methods: The 2008 Health Survey for England data were used with 1,109 participants aged ≥18 years providing complete data. MVPA time was assessed using an accelerometer. Weighted linear regression models quantified the continuous associations of MVPA and BMI with HbA1c. Interaction analyses were implemented to observe whether the association of MVPA with HbA1c was modified by BMI or vice versa. In order to assess the categorical associations of MVPA and BMI with HbA1c, participants were classified into one of four categories: (1) 'physically active & non-obese', (2) 'physically active & obese', (3) 'physically inactive & non-obese', and (4) 'physically inactive & obese'. 'Physically active' was defined as: ≥150 minutes/week of MVPA. 'Obese' was defined as: BMI ≥30.0 kg/m^2. Linear regression analyses examined the differences in HbA1c across the derived categories.

Results: In the maximally adjusted model, every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.07% (p<0.001)] lower HbA1c level. Each 1 kg/m^2 increment in BMI was associated with a 0.2 mmol/mol [0.02% (p<0.001)] higher HbA1c level. The association of MVPA with HbA1c was stronger in obese individuals (-1.5 mmol/mol [-0.13% (p<0.001)]) than non-obese individuals (-0.7 mmol/mol [-0.06% (p<0.001)]); p=0.004 for interaction. The association of BMI with

HbA1c remained stable across MVPA categories. Compared to individuals categorised as 'physically inactive & obese', only those categorised as 'physically active & obese' or 'physically active & non-obese' had lower HbA1c levels by 2.1 mmol/mol [0.19% (p=0.005)] and 3.5 mmol/mol [0.32% (p<0.001)], respectively. **Conclusions:** This study further emphasises the importance of physical activity, particularly in obese adults, with clinical relevance for national diabetes prevention programmes assessed by HbA1c.

Keywords: Type 2 Diabetes Mellitus; Glycated Haemoglobin; Body Mass Index; Obesity; Moderate-to-Vigorous-Intensity Physical Activity; Epidemiology

Abbreviations: Type 2 Diabetes Mellitus (T2DM); Glycated Haemoglobin (HbA1c); Moderate-to-Vigorous-Intensity Physical Activity (MVPA); Body Mass Index (BMI); Health Survey for England (HSE); National Health Service (NHS); Oral Glucose Tolerance Test (OGTT); Standard Deviation (SD)

ARTICLE SUMMARY

Strengths and limitations of this study

- The effects of lifestyle interventions on glycated haemoglobin (HbA1c), a validated and clinically employed measure of diabetes risk, are well-defined in populations with type 2 diabetes; however, they are less clear in the general population.
- Here, we investigated the independent and combined associations of objectively measured moderate-to-vigorous-intensity physical activity (MVPA) and body mass index (BMI) with HbA1c in a national sample of adults.
- This study highlights the potential importance of physical activity in maintaining healthy HbA1c levels in obese populations.
- The cross-sectional design eliminates the possibility of establishing causality.

INTRODUCTION

Diabetes mellitus is one of the most prevalent and costly chronic conditions accounting for between 7-14% of health care funding globally.[1] This health care burden is projected to continue rising into the future.[2] Type 2 diabetes mellitus (T2DM), the most common form of the condition, is consequently recognised as a health care priority. Given T2DM is predominantly a lifestyle-related chronic condition and that lifestyle interventions have consistently been shown to reduce the risk of T2DM across a range of diverse populations,[3] prevention strategies are largely focused on the promotion of healthy behaviours. In England, the National Health Service (NHS) has recently identified the prevention of T2DM as a leading priority and commissioned a national diabetes prevention programme based on behavioural counselling and lifestyle intervention for those at high risk.[4]

Revisions to the diagnostic criteria for T2DM in 2011 to include glycated haemoglobin (HbA1c),[5] a measure of glycaemia that reflects average glucose concentrations over the previous 2-3 months, precipitated clinical changes more widely in the assessment of metabolic health. While glucose control was historically assessed by a 'gold standard' oral glucose tolerance test (OGTT), HbA1c is easier to assess and is increasingly being used to identify and refer high risk populations into prevention programmes and to monitor the impact of lifestyle interventions.[4-6] However, whilst the effects of lifestyle interventions on HbA1c are well-defined in populations with T2DM,[7-9] they are less clear in populations without diabetes; where OGTT measures have dominated the literature.[10] This has limited the ability to quantify or model the potential differences in HbA1c gained through targeting

specific common lifestyle factors and behavioural targets within the general population and their likely interaction.

Physical inactivity and excess adiposity have consistently been independently associated with an increased risk of chronic disease and have formed key targets within diabetes prevention programmes.[11] In this study, we use data from a national survey to quantify the independent and combined associations of objectively measured moderate-to-vigorous-intensity physical activity (MVPA) and body mass index (BMI) with HbA1c in the general population.

METHODS

Study sample

The Health Survey for England (HSE) is a series of national annual surveys designed to examine the health and well-being of people living in England.[12 13] In order to obtain a population-based sample, these cross-sectional surveys employ a multistage stratified random sampling procedure. The 2008 wave of the HSE was centred on physical activity and fitness and included a subset of participants who were asked to wear an accelerometer for the objective assessment of physical activity.[12 13] In total, accelerometer data on 2,313 adults (aged ≥18 years) were available, with 2,131 adults providing valid accelerometer data (see online supplementary materials - Figure S1). Participants provided written informed consent. Ethical approval for the 2008 HSE survey was obtained from the Oxford A Research Ethics Committee (reference number: 07/H0604/102). Further details are reported elsewhere.[12 13]

Physical activity

Physical activity and sedentary time were measured using an ActiGraph GT1M accelerometer (ActiGraph Corporation, Pensacola, Florida, USA) which was worn on the right hip for seven consecutive days during waking hours (except water-based activities).[12] The ActiGraph GT1M device was initialised to collect data using one minute epochs. Accelerometer files were processed using KineSoft V3.3.76 (KineSoft, Loughborough, UK). Accelerometer counts were used to calculate the total time spent in MVPA (≥1952 counts/minute), light-intensity physical activity (≥100 to <1952 counts/minute) and sedentary behaviour (<100 counts/minute).[14 15] Non-wear time was defined as any periods of continuous zero counts for ≥60 consecutive minutes.[16] Valid accelerometry data were defined as ≥10 hours of wear-time per day with ≥4 days of data. The average number of minutes per valid day spent in each intensity band were calculated.

Whilst time in total accumulated MVPA was used for the primary analysis, MVPA time accumulated in bouts of ≥10 minutes (allowing for a two minute exception in the intensity threshold) was also derived for a sensitivity analysis (see *Statistical analysis - Sensitivity analysis*).

BMI

A trained fieldworker recorded height (measured to the nearest 0.1 cm) and weight (measured to the nearest 0.1 kilogram using an electronic scale) readings.[13] BMI was calculated as the weight (in kilograms) divided by the square of the height (in metres).

Waist circumference

Waist circumference was defined as the midpoint between the lower rib and the upper boundary of the iliac crest. A nurse measured this twice to the nearest 0.1 cm using a tape and the average of the two readings was used.[13] This variable was included as differences in lean mass may exaggerate findings for physically active and obese individuals under the BMI measure. Therefore, sensitivity analyses replacing BMI with waist circumference were executed (see *Statistical analysis - Sensitivity analysis*).

HbA1c

Non-fasting blood samples were collected by a nurse for the analysis of HbA1c.[13] Blood analytes were assayed at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, England. Further details are reported elsewhere.[12 13] Data on HbA1c are reported in dual units: mmol/mol (to one decimal place) and % (to two decimal places).

Contextual variables

The following factors, collected by a trained fieldworker, were also utilised: age (in years); disease index (no diseases, one or more diseases); ethnicity (white, non-white); reported fruit and vegetable consumption (0, 1-3, 4-6, 7+ portions/day); income (low, intermediate, high); sex (men, women); smoking status (never smoked, ex-smoker, current smoker); socioeconomic status (national statistics socioeconomic classification: high, high-intermediate, intermediate, low intermediate, low); and any prescribed medication (no, yes). The 'disease index' variable was based on

physician diagnosed conditions/illnesses relating to the following systems: blood and related organs; digestive; ear; endocrine and metabolic; eye; genitourinary; heart and circulatory; infectious and parasitic; mental disorders; musculoskeletal; neoplastic; nervous; respiratory; skin; and any other structure. Further details are reported elsewhere.[12 13]

Statistical analysis

All statistical analyses were conducted using Stata/IC V14.0 (Stata Corporation, College Station, Texas, USA) and controlled for the complex survey strategy employed in the 2008 HSE (primary sampling units, clustering and survey weights) in order to produce estimates representing the national population.[12 13]

Covariate selection and missing data

Multiple linear regression models were used to assess the associations between measures of total accumulated MVPA time and BMI with HbA1c after the adjustment for confounders. Confounders were considered for inclusion as follows: primarily using all the available data, in separate models for MVPA and BMI with HbA1c as the dependent variable, confounders were included based on a criteria of changing the regression coefficient for either MVPA or BMI by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time.[17] The confounders examined included: income, socioeconomic status, disease index, any prescribed medication, smoking status, reported fruit and vegetable consumption, light-intensity physical activity time and sedentary time. Of these, only income and any prescribed medication affected the relationships of MVPA and BMI with HbA1c (see online supplementary materials - Table S1), and were therefore

included as confounders in all analyses. A complete-case analysis was used for handling any missing data (BMI (n=185), HbA1c (n = 746) and covariate: income (n = 334)). In total 1,109 adults provided valid accelerometer data with complete BMI, HbA1c and covariate (age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time) data and were included for analysis (see online supplementary materials - Figure S1). The weighted prevalence (n (%)) of the English adults in each category were computed. Participant characteristics of the full sample, stratified by each category, were tabulated. Categorical variables were presented as numbers and proportions, whereas continuous variables were summarised as means and standard deviations.

Continuous measures

Model 1, examining the associations between continuous measures of total accumulated MVPA time or BMI with HbA1c, adjusted for: age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time. Model 2 additionally adjusted for BMI (for MVPA analysis) and MVPA (for BMI analysis). Interaction analyses investigated if results for MVPA and BMI were modified by sex and age, and whether the association of MVPA with HbA1c was modified by BMI or vice-versa.

Categorical measures

For descriptive purposes and to investigate the separate and combined associations of physical activity and obesity, a multiple linear regression model was fitted to analyse the differences in HbA1c between categories of total accumulated MVPA time and BMI. To mirror national and international guidance,[18 19] MVPA status was

classified as 'physically active' or 'physically inactive' on the basis of whether or not participants accumulated a total of ≥150 minutes/week of MVPA, respectively. BMI status was determined as 'non-obese' or 'obese' on the basis of a BMI threshold of 30.0 kg/m^2 (i.e. non-obese if BMI <30.0 kg/m^2 and obese if BMI ≥30.0 kg/m^2). These categories allowed four mutually exclusive groups: (1) 'physically active & non-obese', (2) 'physically active & obese', (3) 'physically inactive & non-obese', and (4) 'physically inactive & obese'. The 'physically inactive and obese' category was selected as the reference group as it was hypothesised *a priori* to be the least desirable state. The model adjusted for all the covariates stated previously (i.e. age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time).

All reported p-values were two-sided, and in order to account for multiple comparisons, p<0.01 was considered to be statistically significant for the main effects. For interaction analyses, p<0.05 was considered to be statistically significant. Results for the regression analyses are presented as mean differences (99% confidence intervals) in HbA1c.

Sensitivity analysis

In order to examine the robustness of the reported associations, the following sensitivity analyses were conducted: (1) BMI was replaced with waist circumference (presented as 1 cm increments) in all described investigations with categorical data defined as 'obese' (≥102 cm for men and ≥88 cm for women) or 'non-obese' (<102 cm for men and <88 cm for women); (2) 'Obese' was defined as having a BMI of ≥27.5 kg/m^2 for the categorical data; and (3) Participants were only classified into the

'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes for the categorical data.

RESULTS

Participant characteristics

Table 1 displays the characteristics of the included 1,109 participants [mean age (standard deviation (SD)) = 51.0 (16.5) years; mean BMI (SD) = 27.3 (4.8) kg/m^2; mean total accumulated MVPA time (SD) = 30.8 (25.8) minutes] across derived categories of MVPA and BMI.

Associations of physical activity and body mass index with glycated haemoglobin

Table 1 - Descriptive characteristics of the 1,109 participants included for analysis summarised overall and by physical activity and obesity status

Characteristic		Sample	'Physically active & non-obese'	'Physically active & obese'	'Physically inactive & non-obese'	'Physically inactive & obese'
		N = 1,109	n = 493; 45.9%	n = 118; 10.7%	n = 343; 29.9%	n = 155; 13.5%
Age (years) †		51.0 (16.5)	46.0 (14.7)	51.1 (13.2)	55.2 (18.4)	58.4 (15.0)
Body Mass Index (kg/m^2) †		27.3 (4.8)	25.1 (2.7)	33.4 (3.0)	25.5 (3.2)	34.3 (3.9)
By Sex:	Men	27.6 (4.2)	25.4 (2.6)	33.3 (2.5)	26.3 (2.6)	34.2 (3.1)
	Women	27.0 (5.4)	24.6 (2.9)	33.5 (3.6)	24.8 (3.4)	34.4 (4.4)
Waist Circumference (cm) †		92.9 (13.9)	87.3 (10.5)	106.9 (9.5)	89.6 (12.2)	109.1 (11.3)
By Sex:	Men	98.4 (12.1)	92.2 (9.0)	112.0 (7.6)	97.6 (9.4)	114.1 (9.0)
	Women	87.2 (13.5)	81.1 (8.9)	101.2 (7.9)	83.3 (10.1)	104.8 (11.4)
Ethnicity ‡						
White		1,055 (94.2)	470 (94.7)	112 (94.3)	324 (93.4)	149 (94.7)
Non-White		54 (5.8)	23 (5.3)	6 (5.7)	19 (6.6)	6 (5.3)
Income ‡						
Low		287 (24.0)	92 (16.7)	31 (24.3)	111 (30.6)	53 (33.5)
Intermediate		364 (33.5)	159 (32.9)	43 (38.5)	107 (32.0)	55 (35.6)
High		458 (42.5)	242 (50.4)	44 (37.2)	125 (37.4)	47 (30.9)

Associations of physical activity and body mass index with glycated haemoglobin

Sex ‡					
Men	523 (50.2)	257 (55.4)	60 (53.5)	142 (43.5)	64 (45.0)
Women	586 (49.8)	236 (44.6)	58 (46.5)	201 (56.5)	91 (55.0)
Any Prescribed Medication ‡					
No	503 (47.7)	278 (58.0)	57 (49.3)	129 (40.1)	39 (28.5)
Yes	606 (52.3)	215 (42.0)	61 (50.7)	214 (59.9)	116 (71.5)
Accelerometer Wear-Time † (no. of minutes/valid day)	867.7 (72.1)	873.2 (68.9)	870.4 (77.1)	854.9 (74.7)	875.1 (69.3)
Total Accumulated Moderate-to-Vigorous-Intensity Physical Activity Time † (no. of minutes/valid day)	30.8 (25.8)	47.2 (25.5)	41.3 (18.6)	11.5 (6.4)	9.7 (5.9)
Moderate-to-Vigorous-Intensity Physical Activity Time in Bouts of ≥10 Minutes † (no. of minutes/valid day)	10.8 (16.2)	39.8 (22.0)	36.4 (11.7)	5.6 (6.1)	4.5 (5.8)
Number of Valid Days ‡					
4	46 (4.5)	17 (3.9)	9 (8.0)	12 (3.5)	8 (6.1)
5	80 (7.5)	32 (6.7)	5 (4.3)	31 (9.3)	12 (8.5)
6	209 (19.7)	89 (18.4)	20 (18.0)	77 (24.1)	23 (15.8)
7	774 (68.3)	355 (71.0)	84 (69.7)	223 (63.1)	112 (69.6)
Glycated Haemoglobin (HbA1c)					
[mmol/mol] †	38.1 (7.3)	36.1 (4.9)	38.5 (4.8)	39.2 (9.2)	41.9 (8.7)
[%] †	5.63 (0.67)	5.45 (0.45)	5.67 (0.44)	5.74 (0.84)	5.98 (0.79)

All analyses controlled for primary sampling units, clustering and survey weights.

† *Continuous variable; Mean (Standard Deviation)*

‡ *Categorical variable; n (Proportion (%))*

346

347

348 **Continuous measures**

Table 2 displays the associations between continuous measures of total accumulated MVPA time, BMI and HbA1c. In the maximally adjusted model, every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.07% (p<0.001)] lower HbA1c level. Each 1 kg/m^2 increment in BMI was associated with a 0.2 mmol/mol [0.02% (p<0.001)] higher HbA1c level. Results were not modified by age (p=0.104 for age x MVPA interaction; p=0.300 for age x BMI interaction) or sex (p=0.975 for sex x MVPA interaction; p=0.170 for sex x BMI interaction). However, the MVPA x BMI interaction term was significant (p=0.004) for the association with HbA1c. Table 3 highlights the association of MVPA with HbA1c stratified by BMI status, and the association of BMI with HbA1c stratified by MVPA status. The association of MVPA with HbA1c was stronger in obese individuals, where every 30 minutes/day increment in MVPA was associated with a 1.5 mmol/mol [0.13% (p<0.001)] lower HbA1c level. In non-obese individuals, every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.06% (p<0.001)] lower HbA1c level. In contrast, the association of BMI with HbA1c remained stable across MVPA categories.

Associations of physical activity and body mass index with glycated haemoglobin

Table 2 - Adjusted linear regression models showing the continuous associations of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and body mass index (BMI) with glycated haemoglobin (HbA1c)

Adjusted linear regression model	HbA1c (dual units)	MVPA (30 minutes/day)		BMI (1 kg/m^2)	
		Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
Model 1	[mmol/mol] [%]	**-0.9 (-1.4, -0.4)** **-0.08 (-0.13, -0.04)**	**<0.001**	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**
Model 2	[mmol/mol] [%]	**-0.7 (-1.2, -0.2)** **-0.07 (-0.11, -0.02)**	**<0.001**	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**

*All analyses controlled for primary sampling units, clustering and survey weights. **Bold** indicates statistical significance at p<0.01. Model 1 adjusted for: age; ethnicity; income; sex; any prescribed medication; and accelerometer wear-time. Model 2 additionally adjusted for BMI (for MVPA analysis) and MVPA (for BMI analysis).*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m^2 increment in BMI*

Associations of physical activity and body mass index with glycated haemoglobin

370 *Table 3 - Adjusted linear regression models showing the continuous associations of total accumulated moderate-to-vigorous-intensity physical*

371 *activity (MVPA) time and body mass index (BMI) with glycated haemoglobin (HbA1c) stratified by MVPA and BMI levels*

P-value of MVPA x BMI interaction term	Stratification	HbA1c (dual units)	MVPA (30 minutes/day)		BMI (1 kg/m^2)	
			Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
0.004	BMI <30.0 kg/m^2	[mmol/mol]	**-0.7 (-1.2, -0.1)**	**0.002**	-	-
		[%]	**-0.06 (-0.11, -0.01)**			
	BMI ≥30.0 kg/m^2	[mmol/mol]	**-1.5 (-2.3, -0.6)**	**<0.001**	-	-
		[%]	**-0.13 (-0.21, -0.05)**			
	MVPA <150 mins/week	[mmol/mol]	-	-	**0.2 (0.1, 0.3)**	**<0.001**
		[%]			**0.02 (0.01, 0.03)**	
	MVPA ≥150 mins/week	[mmol/mol]	-	-	**0.2 (0.1, 0.3)**	**<0.001**
		[%]			**0.02 (0.01, 0.03)**	

All analyses controlled for primary sampling units, clustering and survey weights. ***Bold*** *indicates statistical significance at p<0.01. Models adjusted for: age; ethnicity; income; sex; any prescribed medication; and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m^2 increment in BMI*

Categorical measures

Table 4 shows the differences in HbA1c levels between categories of total accumulated MVPA time and BMI. Compared with individuals who were 'physically inactive & obese', those who were 'physically active & obese' or 'physically active & non-obese' had significantly lower HbA1c levels by 2.1 mmol/mol [0.19% (p=0.005)] and 3.5 mmol/mol [0.32% (p<0.001)], respectively. However, average HbA1c levels were not significantly different between the 'physically inactive & non-obese' and 'physically inactive and obese' categories.

Associations of physical activity and body mass index with glycated haemoglobin

Table 4 - Adjusted linear regression model showing the categorical associations of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and body mass index (BMI) with glycated haemoglobin (HbA1c)

HbA1c (dual units)	'Physically active & non-obese'		'Physically active & obese'		'Physically inactive & non-obese'		'Physically inactive & obese'
	Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	
[mmol/mol]	**-3.5 (-5.2, -1.9)**	**<0.001**	**-2.1 (-4.1, -0.2)**	**0.005**	-1.9 (-3.8, 0.0)	0.012	Reference
[%]	**-0.32 (-0.47, -0.18)**		**-0.19 (-0.37, -0.02)**		-0.17 (-0.35, 0.00)		

All analyses controlled for primary sampling units, clustering and survey weights.

'Physically active' was defined as: ≥150 minutes/week of total accumulated MVPA.

'Physically inactive' was defined as: <150 minutes/week of total accumulated MVPA.

'Obese' was defined as: BMI ≥30.0 kg/m^2.

'Non-obese' was defined as: BMI <30.0 kg/m^2.

***Bold** indicates statistical significance at p<0.01. Model adjusted for: age; ethnicity; income; sex; any prescribed medication; and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) in comparison to the 'physically inactive and obese' category*

Sensitivity analysis

Sensitivity analyses indicated robustness. When waist circumference was used in place of BMI, the pattern of results was unchanged (see online supplementary materials - Table S2). The results were not modified by age (p=0.069 for age x MVPA interaction; p=0.922 for age x waist circumference interaction) or sex (p=0.923 for sex x MVPA interaction; p=0.483 for sex x waist circumference interaction). However, the pattern of results was exaggerated for the MVPA x waist circumference interaction analysis (p<0.001 for interaction; see online supplementary materials - Table S3). In those with high waist circumference, every 30 minutes/day increment in MVPA was associated with a 1.8 mmol/mol [0.16% (p<0.001)] lower HbA1c level. The other sensitivity analyses also indicated stability; although the prevalence in each category varied across the different methods used (see online supplementary materials - Table S4), the key findings were largely unaffected (see online supplementary materials - Table S5).

DISCUSSION

This study quantified the independent and combined associations of objectively measured MVPA and BMI with HbA1c in a nationally representative sample of adults. Both MVPA and BMI were independently associated with HbA1c; every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.07%] lower HbA1c level and each 1 kg/m^2 increment in BMI was associated with a 0.2 mmol/mol [0.02%] higher HbA1c level. Results for MVPA were modified by BMI status, with a stronger association seen in obese individuals. For those with a BMI of 30.0 kg/m^2 or

higher, every 30 minutes/day increment in MVPA was associated with a 1.5 mmol/mol [0.13%] lower HbA1c level.

Whilst intervention studies have established and quantified the effects on HbA1c levels following interventions aimed at increasing physical activity or reducing body weight in individuals with T2DM,[7-9] the associations between these factors in the general population are less clear. This is an important limitation as diabetes prevention recommendations and programmes within routine care are increasingly moving towards identifying and referring individuals on the basis of HbA1c whilst also evaluating effectiveness through changes to HbA1c.[4-6] The latter point is particularly important as there is a lack of data supporting the magnitude of potential differences in HbA1c anticipated with specific differences in health behaviours.

Our findings extend previous research using HSE data which have reported an association between MVPA and HbA1c in a subsample of older adults.[20] The study also found that neither self-reported or accelerometer assessed sedentary time was associated with HbA1c. Others have also reported a lack of association between sedentary time and HbA1c in HSE using both objective and self-reported data.[21] However, previous studies using HSE did not examine the independent association or modifying effect of BMI. This contrasts with the strong and consistent association reported in the present study for MVPA, suggesting that MVPA may be the stronger determinant of HbA1c in HSE. Our findings are also are consistent with analyses of NHANES which have shown that there was no statistical difference in HbA1c between active obese adults and inactive normal weight adults, with a further analysis showing that an association between MVPA and HbA1c was only present in

those with a moderate or high risk of type 2 diabetes;[22 23] however, neither of these studies formally tested for an interaction with BMI. By showing the association of MVPA with HbA1c is stronger in obese adults, our results suggest that MVPA may have greater potential to moderate glycaemic status at higher levels of BMI and confirms previous research suggesting that active obese adults have healthier levels of HbA1c than inactive obese adults. The difference in HbA1c for every 30 minutes/day increment in MVPA observed for obese individuals in our study is likely to be clinically meaningful beyond diabetes risk. For example, in adults without diabetes, each 0.1% unit increment in HbA1c has been associated with a 2% higher risk of mortality and a 4% higher risk of coronary heart disease or stroke.[24]

Our finding that MVPA may be metabolically protective in obese individuals is also consistent with studies that have shown that cardiorespiratory fitness, which is partly moderated by MVPA, is also an important determinant of metabolic health in obesity.[25] Other studies have consistently reported that obese individuals with moderate to high fitness have a lower risk of all-cause and cardiovascular mortality those with normal BMI but low fitness.[26] However, the extent to which MVPA and fitness can reduce the excess risks of obesity remains controversial,[27] supporting the need for further research in this area. Our results are supported by intervention studies and known mechanistic pathways linking reduced adiposity and higher physical activity to better glucose control and reduced insulin resistance.[3 28-31] The impact of physical activity on glucose levels and insulin resistance in obesity may also be enhanced by preferentially shifting the storage of excess fat away from metabolically active sites, such as within visceral compartments or organs, without effecting overall level adiposity.[32]

Strengths and limitations

Our study has several strengths, which include: exploitation of a well-characterised national survey which employs a multifaceted stratified random sampling procedure; examining age and sex interactions; and a range of sensitivity analyses. The key limitation resides in the cross-sectional design which eliminates the possibility of establishing causality. In addition, although we adjusted for a wide range of important lifestyle, demographic and clinical variables, it is possible that unmeasured factors were confounding the reported associations. The amount of missing biochemical data could also act to limit generalizability. In addition, although the inclusion of objective MVPA is a notable strength, the device used also has some limitations. Reliance on vertical accelerations to quantify movement and lack of waterproofing means that some activities like cycling may not have been adequately captured whereas others like swimming were not captured at all. However, ambulation, which makes up the vast majority of human movement, is accurately assessed by accelerometers. Furthermore, cycling and swimming can be considered to be atypical activities in this cohort; with only a small proportion of participants reporting any cycling or swimming activities at all.[12]

Conclusions

In conclusion, this study quantifies the association between MVPA, BMI and HbA1c and shows that the association of MVPA with HbA1c is stronger in those with higher BMI levels. Finding ways of translating this information into encouraging obese people to increase their physical activity levels as an intervention for lowering HbA1c

might be important to improve public health and allow for more personalised educational and lifestyle interventions to be implemented. However, given the limitations which preclude inferences of causality, these conclusions need to be confirmed by interrogating data from completed diabetes prevention trials or through further experimental studies.

DECLARATIONS

Ethics approval and consent to participate

Ethical approval for the 2008 Health Survey for England study was obtained from the Oxford A Research Ethics Committee (reference number: 07/H0604/102). Participants provided written informed consent.

Data sharing statement

Permission to use the 2008 Health Survey for England accelerometer data files can be obtained from the National Centre for Social Research (NatCen) (http://www.natcen.ac.uk/). All other data are openly available to download from the UK Data Archive (https://discover.ukdataservice.ac.uk/series/?sn=2000021).

Competing interests

SJHB: Funding has been received since 2012 for consultancy work from Fitness First, Nuffield Health, Unilever, and Weight Watchers, and for travel from The Coca Cola Foundation. None of these are currently active. Funding was received in 2016 for consultancy work for Halpern Limited. A sit-to-stand desk was kindly provided by Ergotron from 2012-2014. Advice has been requested by and offered to Active Working and Get Britain Standing. TY, MJD and KK: Developed a prevention programme, Let's Prevent Diabetes, selected to be part of Healthier You: The NHS Diabetes Prevention Programme in collaboration with Ingeus UK Limited. KK also chaired NICE guidance for the prevention of type 2 diabetes mellitus (PH 38), with TY and MJD part of the committee. All other authors declare that they have no competing interests.

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Authors' contributions

TY had the original idea for the analysis, which was further developed and refined by KB, CLE, DHB, DWE, JMRG, AK, LV, AJS, NS, SJHB, MH, MJD and KK. CLE processed the 2008 Health Survey for England accelerometer data. KB carried out the statistical analysis and worked with TY to write the first and revised drafts of the manuscript. KB, TY, CLE, DHB, DWE, JMRG, AK, LV, AJS, NS, SJHB, MH, MJD and KK edited and reviewed the manuscript drafts. KB, TY, CLE, DHB, DWE, JMRG, AK, LV, AJS, NS, SJHB, MH, MJD and KK approved the final version of the manuscript.

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Research Unit (NIHR DLPA BRU) based at University Hospitals of Leicester and Loughborough University, the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC – EM) and the Leicester Clinical Trials Unit (LCTU). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health (DoH).

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SUPPLEMENTARY MATERIALS

Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin within the general population: a cross-sectional analysis of Health Survey for England

Authors: Kishan Bakrania*, Thomas Yates*, Charlotte L. Edwardson, Danielle H. Bodicoat, Dale W. Esliger, Jason M.R. Gill, Aadil Kazi [2, 3], Latha Velayudhan, Alan J. Sinclair, Naveed Sattar, Stuart J.H. Biddle, Mark Hamer, Melanie J. Davies and Kamlesh Khunti

* = joint first authors

Corresponding author: Dr. Charlotte L. Edwardson, Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, Leicestershire, LE5 4PW, United Kingdom. Phone: +44(0)116 258 8577. Email: ce95@le.ac.uk.

Number of supplementary figures: 1

Figure S1 - Flow chart of study participants

Number of supplementary tables: 5

Table S1 - Confounder analysis based on a criteria of changing the regression coefficient for either total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time or body mass index (BMI) by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time

Table S2 - Sensitivity analyses: adjusted linear regression models showing the continuous associations of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c)

Table S3 - Sensitivity analyses: adjusted linear regression models showing the continuous associations of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c) stratified by MVPA and waist circumference levels

Table S4 - Sensitivity analyses: weighted mutually exclusive category prevalence

Table S5 - Sensitivity analyses: adjusted linear regression models showing the categorical associations of moderate-to-vigorous-intensity physical activity (MVPA) time and obesity status with glycated haemoglobin (HbA1c)

Figure S1 - Flow chart of study participants

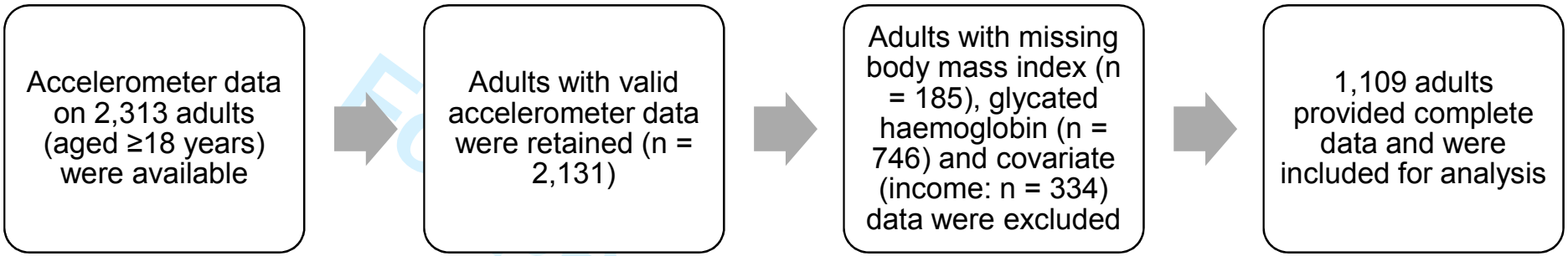

Table S1 - Confounder analysis based on a criteria of changing the regression coefficient for either total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time or body mass index (BMI) by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time

		MVPA (30 minutes/day): Beta †	% Change in MVPA Beta	BMI (1 kg/m^2): Beta ‡	% Change in BMI Beta
HbA1c (dual units)	[mmol/mol]	-1.08619	-	0.27118	-
	[%]	-0.09939		0.02481	
Covariate individually added to basic model (age, sex, ethnicity and accelerometer wear-time)					
Disease index		-1.00775 -0.09221	7.2	0.26435 0.02419	-2.5
Reported fruit & vegetable consumption		-1.09698 -0.10037	-1.0	0.26803 0.02452	-1.2
Income		-1.06915 -0.09783	1.6	**0.23041** **0.02108**	**-15.0**
Smoking status		-1.05337 -0.09638	3.0	0.28741 0.02630	6.0
Socioeconomic status		-1.15279 -0.10548	-6.1	0.26994 0.02470	-0.5
Any prescribed medication		**-0.97137** **-0.08888**	**10.6**	0.25601 0.02343	-5.6

Sedentary time	-1.18817 -0.10872	-9.4	0.27013 0.02472	-0.4
Light-intensity physical activity time	-1.11946 -0.10243	-3.1	0.27152 0.02484	0.1

All analyses controlled for primary sampling units, clustering and survey weights. Confounders were considered for inclusion as follows: primarily using all the available data, in separate models for MVPA and BMI with glycated haemoglobin (HbA1c) as the dependent variable, confounders were included based on a criteria of changing the regression coefficient for either MVPA or BMI by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time. ***Bold*** *indicates a ≥10% change in the regression coefficient for either MVPA or BMI.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m^2 increment in BMI*

Table S2 - Sensitivity analyses: adjusted linear regression models showing the continuous associations of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c)

Adjusted linear regression model	HbA1c (dual units)	MVPA (30 minutes/day)		Waist Circumference (1 cm)	
		Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
Model 1	[mmol/mol] [%]	**-0.9 (-1.4, -0.4)** **-0.08 (-0.13, -0.03)**	**<0.001**	**0.1 (0.1, 0.1)** **0.01 (0.01, 0.01)**	**<0.001**
Model 2	[mmol/mol] [%]	**-0.6 (-1.0, -0.1)** **-0.05 (-0.10, -0.01)**	**0.003**	**0.1 (0.1, 0.1)** **0.01 (0.01, 0.01)**	**<0.001**

*All analyses controlled for primary sampling units, clustering and survey weights. **Bold** indicates statistical significance at p<0.01. Model 1 adjusted for: age; ethnicity; income; sex; any prescribed medication; and accelerometer wear-time. Model 2 additionally adjusted for waist circumference (for MVPA analysis) and MVPA (for waist circumference analysis).*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 cm increment in waist circumference*

Table S3 - Sensitivity analyses: adjusted linear regression models showing the continuous associations of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c) stratified by MVPA and waist circumference levels

P-value of MVPA x Waist Circumference interaction term	Stratification	HbA1c (dual units)	MVPA (30 minutes/day)		Waist Circumference (1 cm)	
			Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
<0.001	Low Waist Circumference	[mmol/mol] [%]	-0.3 (-0.7, 0.0) -0.03 (-0.06, 0.00)	0.024	-	-
	High Waist Circumference	[mmol/mol] [%]	**-1.8 (-3.0, -0.5)** **-0.16 (-0.28, -0.05)**	**<0.001**	-	-
	MVPA <150 mins/week	[mmol/mol] [%]	-	-	**0.1 (0.1, 0.2)** **0.01 (0.01, 0.02)**	**<0.001**
	MVPA ≥150 mins/week	[mmol/mol] [%]	-	-	**0.1 (0.0, 1)** **0.01 (0.00, 0.01)**	**<0.001**

All analyses controlled for primary sampling units, clustering and survey weights. 'High Waist Circumference' was defined as having a waist circumference of ≥102 cm for men and ≥88 cm for women. ***Bold*** *indicates statistical significance at p<0.01. Models adjusted for: age; ethnicity; income; sex; any prescribed medication; and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 cm increment in waist circumference*

Table S4 - Sensitivity analyses: weighted mutually exclusive category prevalence

	Weighted Prevalence [%]			
Method	'Physically active & non-obese'	'Physically active & obese'	'Physically inactive & non-obese'	'Physically inactive & obese'
Reference	45.9%	10.7%	29.9%	13.5%
1	37.8%	19.0%	20.0%	23.2%
2	36.1%	20.5%	20.7%	22.7%
3	14.3%	1.8%	61.5%	22.4%

All analyses controlled for primary sampling units, clustering and survey weights.

Reference Method = Mutually exclusive categories derived and utilised in the main analysis

Method 1 = 'Obese' was defined as having a waist circumference of ≥102 cm for men and ≥88 cm for women

Method 2 = 'Obese' was defined as having a body mass index of ≥27.5 kg/m^2

Method 3 = Participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes

Table S5 - Sensitivity analyses: adjusted linear regression models showing the categorical associations of moderate-to-vigorous-intensity physical activity (MVPA) time and obesity status with glycated haemoglobin (HbA1c)

Method	HbA1c (dual units)	'Physically active & non-obese'		'Physically active & obese'		'Physically inactive & non-obese'		'Physically inactive & obese'
		Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	
Reference	[mmol/mol]	**-3.5 (-5.2, -1.9)**	**<0.001**	**-2.1 (-4.1, -0.2)**	**0.005**	-1.9 (-3.8, 0.0)	0.012	Reference
	[%]	**-0.32 (-0.47, -0.18)**		**-0.19 (-0.37, -0.02)**		-0.17 (-0.35, 0.00)		
1	[mmol/mol]	**-4.1 (-5.9, -2.2)**	**<0.001**	**-2.5 (-4.4, -0.6)**	**0.001**	**-3.1 (-5.0, -1.2)**	**<0.001**	Reference
	[%]	**-0.37 (-0.54, -0.21)**		**-0.23 (-0.40, -0.05)**		**-0.29 (-0.46, -0.11)**		
2	[mmol/mol]	**-2.9 (-4.1, -1.7)**	**<0.001**	**-1.5 (-2.9, -0.2)**	**0.004**	-0.9 (-2.9, 1.1)	0.229	Reference
	[%]	**-0.27 (-0.38, -0.16)**		**-0.14 (-0.27, -0.02)**		-0.08 (-0.27, 0.01)		
3	[mmol/mol]	**-3.4 (-4.7, -2.1)**	**<0.001**	-2.0 (-4.3, 0.3)	0.027	**-1.7 (-3.0, -0.4)**	**0.001**	Reference
	[%]	**-0.31 (-0.43, -0.20)**		-0.18 (-0.39, 0.03)		**-0.16 (-0.28, -0.04)**		

All analyses controlled for primary sampling units, clustering and survey weights.

Reference Method = Mutually exclusive categories derived and utilised in the main analysis

Method 1 = 'Obese' was defined as having a waist circumference of ≥102 cm for men and ≥88 cm for women

Method 2 = 'Obese' was defined as having a body mass index of ≥27.5 kg/m^2

Method 3 = Participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes

***Bold** indicates statistical significance at p<0.01. Models adjusted for: age; ethnicity; income; sex; any prescribed medication; and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) in comparison to the 'physically inactive and obese' category*

STROBE Statement - Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	8-11
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-11
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-11
Bias	9	Describe any efforts to address potential sources of bias	8, 11
Study size	10	Explain how the study size was arrived at	8, 11-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11-14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11-14
		(*b*) Describe any methods used to examine subgroups and interactions	12-14
		(*c*) Explain how missing data were addressed	11-12
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	11
		(*e*) Describe any sensitivity analyses	13-14
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, 11-12
		(b) Give reasons for non-participation at each stage	8, 11-12
		(c) Consider use of a flow diagram	8, 12
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	14-16
		(b) Indicate number of participants with missing data for each variable of interest	12
Outcome data	15*	Report numbers of outcome events or summary measures	14-16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17-18
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done - e.g. analyses of subgroups and interactions, and sensitivity analyses	17-22
Discussion			
Key results	18	Summarise key results with reference to study objectives	22-23
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	25
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	23-24
Generalisability	21	Discuss the generalisability (external validity) of the study results	23-25
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	28

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin within the general population: a cross-sectional analysis of the 2008 Health Survey for England

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Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin within the general population: a cross-sectional analysis of the 2008 Health Survey for England

Authors: Kishan Bakrania* [1, 2, 3, 4], Thomas Yates* [2, 3], Charlotte L. Edwardson [2, 3], Danielle H. Bodicoat [2, 4], Dale W. Esliger [3, 5], Jason M.R. Gill [6], Aadil Kazi [2, 3], Latha Velayudhan [7, 8], Alan J. Sinclair [9], Naveed Sattar [6], Stuart J.H. Biddle [10], Mark Hamer [3, 5], Melanie J. Davies [2, 3] and Kamlesh Khunti [2, 4]

* = joint first authors

[1] Department of Health Sciences, University of Leicester, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[2] Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[3] National Institute for Health Research (NIHR) Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit (BRU), Diabetes Research Centre, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[4] National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care – East Midlands (CLAHRC – EM), Diabetes Research Centre, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

Associations of physical activity and body mass index with glycated haemoglobin

[5] School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, Leicestershire, LE11 3TU, United Kingdom.

[6] British Heart Foundation Glasgow Cardiovascular Research Centre (BHF GCRC), Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, G12 8TA, United Kingdom.

[7] Psychiatry for the Elderly, Department of Health Sciences, University of Leicester, Leicester, Leicestershire, LE1 7RH, United Kingdom.

[8] Older People's Mental Health, Oxleas National Health Service (NHS) Foundation Trust, Bridgeways, Bromley, BR8 2JA, United Kingdom.

[9] Diabetes Frail Ltd, Aston University, Birmingham, West Midlands, B4 7ET, United Kingdom.

[10] Institute of Sport, Exercise & Active Living, Victoria University, Melbourne, VIC 8001, Australia.

Corresponding author: Dr. Charlotte L. Edwardson, Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, Leicestershire, LE5 4PW, United Kingdom. Phone: +44(0)116 258 8577. Email: ce95@le.ac.uk.

Author email addresses: Kishan Bakrania (kb318@le.ac.uk), Thomas Yates (ty20@le.ac.uk), Charlotte L. Edwardson (ce95@le.ac.uk), Danielle H. Bodicoat (dhm6@le.ac.uk), Dale W. Esliger (D.Esliger@lboro.ac.uk), Jason M.R. Gill (Jason.Gill@glasgow.ac.uk), Aadil Kazi (Aadil.Kazi@uhl-tr.nhs.uk), Latha Velayudhan (lv24@le.ac.uk), Alan J. Sinclair (sinclair.5@btinternet.com), Naveed Sattar (Naveed.Sattar@glasgow.ac.uk), Stuart J.H. Biddle

Associations of physical activity and body mass index with glycated haemoglobin

(Stuart.Biddle@vu.edu.au), Mark Hamer (M.Hamer@lboro.ac.uk), Melanie J. Davies (melanie.davies@uhl-tr.nhs.uk) and Kamlesh Khunti (kk22@le.ac.uk).

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ABSTRACT

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Objectives: To investigate the associations of objectively measured moderate-to-vigorous-intensity physical activity (MVPA) and body mass index (BMI) with glycated haemoglobin (HbA1c) in a national sample of English adults.

Methods: The 2008 Health Survey for England data were used with 1,109 participants aged ≥18 years providing complete data. MVPA time was assessed using an accelerometer. Weighted linear regression models, adjusted for several confounders, quantified the associations between continuous measures of MVPA and BMI with HbA1c. Interaction analyses were implemented to observe whether the association of MVPA with HbA1c was modified by BMI or vice versa. Further weighted linear regression models examined the differences in HbA1c across four mutually exclusive categories of MVPA and BMI: (1) 'physically active & non-obese', (2) 'physically active & obese', (3) 'physically inactive & non-obese', and (4) 'physically inactive & obese'. 'Physically active' was defined as: ≥150 minutes/week of MVPA. 'Obese' was defined as: BMI ≥30.0 kg/m^2. A wide range of sensitivity analyses were also implemented.

Results: Every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.07% (p<0.001)] lower HbA1c level. Each 1 kg/m^2 increment in BMI was associated with a 0.2 mmol/mol [0.02% (p<0.001)] higher HbA1c level. The association of MVPA with HbA1c was stronger in obese individuals (-1.5 mmol/mol [-0.13% (p<0.001)]) than non-obese individuals (-0.7 mmol/mol [-0.06% (p<0.001)]); p=0.004 for interaction. The association of BMI with HbA1c remained stable across MVPA categories. Compared to individuals categorised as 'physically inactive &

obese', only those categorised as 'physically active & obese' or 'physically active & non-obese' had lower HbA1c levels by 2.1 mmol/mol [0.19% (p=0.005)] and 3.5 mmol/mol [0.32% (p<0.001)], respectively. Sensitivity analyses indicated robustness and stability.

Conclusions: This study emphasises the importance of physical activity as a determinant of HbA1c, and suggests that the associations may be stronger in obese adults.

Keywords: Type 2 Diabetes Mellitus; Glycated Haemoglobin; Body Mass Index; Obesity; Moderate-to-Vigorous-Intensity Physical Activity; Epidemiology

Abbreviations: Type 2 Diabetes Mellitus (T2DM); Glycated Haemoglobin (HbA1c); Moderate-to-Vigorous-Intensity Physical Activity (MVPA); Body Mass Index (BMI); Health Survey for England (HSE); National Health Service (NHS); Oral Glucose Tolerance Test (OGTT); Standard Deviation (SD)

ARTICLE SUMMARY

Strengths and limitations of this study

- This study utilises glycated haemoglobin (HbA1c) as an outcome, a validated and clinically employed measure of diabetes risk.
- An objective measure of physical activity is employed.
- The cross-sectional design eliminates the possibility of establishing causality.
- The sample used in this study may not be completely representative of the general population.

INTRODUCTION

Diabetes mellitus is one of the most prevalent and costly chronic conditions accounting for between 7-14% of health care funding globally.[1] This health care burden is projected to continue rising into the future.[2] Type 2 diabetes mellitus (T2DM), the most common form of the condition, is consequently recognised as a health care priority. Given T2DM is predominantly a lifestyle-related chronic condition and that lifestyle interventions have consistently been shown to reduce the risk of T2DM across a range of diverse populations,[3] prevention strategies are largely focused on the promotion of healthy behaviours. In England, the National Health Service (NHS) has recently identified the prevention of T2DM as a leading priority and commissioned a national diabetes prevention programme based on behavioural counselling and lifestyle interventions that promote physical activity and weight loss in those at high risk.[4]

Revisions to the diagnostic criteria for T2DM in 2011 to include glycated haemoglobin (HbA1c),[5] an easy to assess and increasingly used measure of glycaemia that reflects average glucose concentrations over the previous 2-3 months, precipitated clinical changes more widely in the assessment of metabolic health.[4-6] However, whilst the effects of physical activity and weight loss on HbA1c are well-defined in populations with T2DM,[7-9] they are less clear in populations without diabetes.[10]

In this study, we use data from a national survey to quantify the associations of objectively measured moderate-to-vigorous-intensity physical activity (MVPA) and body mass index (BMI) with HbA1c in the general population, and observe whether

the association of MVPA with HbA1c is modified by BMI or vice versa. Here, we hypothesize that MVPA may provide a metabolically protective effect in obese individuals; since cardiorespiratory fitness, a factor that is partly moderated by MVPA, has previously been shown to be an important determinant of metabolic health in obesity.[11] We also examine the differences in HbA1c across mutually exclusive categories of MVPA and BMI.

METHODS

Study sample

The Health Survey for England (HSE) is a series of national annual surveys designed to examine the health and well-being of people living in England.[12 13] In order to obtain a population-based sample, these cross-sectional surveys employ a multistage stratified random sampling procedure. The 2008 wave of the HSE was centred on physical activity and fitness and included a subset of participants who were asked to wear an accelerometer for the objective assessment of physical activity.[12 13] In total, accelerometer data on 2,313 adults (aged ≥18 years) were available, with 2,131 adults providing valid accelerometer data (see online supplementary materials - Figure S1). Participants provided written informed consent. Ethical approval for the 2008 HSE survey was obtained from the Oxford A Research Ethics Committee (reference number: 07/H0604/102). Further details are reported elsewhere.[12 13]

Physical activity

Physical activity and sedentary time were measured using an ActiGraph GT1M accelerometer (ActiGraph Corporation, Pensacola, Florida, USA) which was worn on the right hip for seven consecutive days during waking hours (except water-based activities).[12] The ActiGraph GT1M device was initialised to collect data using one minute epochs. Accelerometer files were processed using KineSoft V3.3.76 (KineSoft, Loughborough, UK). Accelerometer counts were used to calculate the total time spent in MVPA (≥1952 counts/minute), light-intensity physical activity (≥100 to <1952 counts/minute) and sedentary behaviour (<100 counts/minute).[14 15] Non-wear time was defined as any periods of continuous zero counts for ≥60 consecutive minutes.[16] Valid accelerometry data were defined as ≥10 hours of wear-time per day with ≥4 days of data. The average number of minutes per valid day spent in each intensity band were calculated.

Whilst time in total accumulated MVPA was used for the primary analysis, MVPA time accumulated in bouts of ≥10 minutes (allowing for a two minute exception in the intensity threshold) was also derived for a sensitivity analysis (see *Statistical analysis - Sensitivity analysis*).

BMI

A trained fieldworker recorded height (measured to the nearest 0.1 cm) and weight (measured to the nearest 0.1 kilogram using an electronic scale) readings.[13] BMI was calculated as the weight (in kilograms) divided by the square of the height (in metres).

Waist circumference

Waist circumference was defined as the midpoint between the lower rib and the upper boundary of the iliac crest. A nurse measured this twice to the nearest 0.1 cm using a tape and the average of the two readings was used.[13] This variable was included as differences in lean mass may exaggerate findings for physically active and obese individuals under the BMI measure. Therefore, sensitivity analyses replacing BMI with waist circumference were executed (see *Statistical analysis - Sensitivity analysis*).

HbA1c

Non-fasting blood samples were collected by a nurse for the analysis of HbA1c.[13] Blood analytes were assayed at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, England. Further details are reported elsewhere.[12 13] Data on HbA1c are reported in dual units: mmol/mol (to one decimal place) and % (to two decimal places).

Covariates

The following factors, collected by a trained fieldworker, were also utilised: age (in years); disease index (no diseases, one or more diseases); ethnicity (white, non-white); reported fruit and vegetable consumption (0, 1-3, 4-6, 7+ portions/day); income (low, intermediate, high); sex (men, women); smoking status (never smoked, ex-smoker, current smoker); socioeconomic status (national statistics socioeconomic classification: high, high-intermediate, intermediate, low intermediate, low); and any prescribed medication (no, yes). The 'disease index' variable was based on physician diagnosed conditions/illnesses relating to the following systems: blood and related organs; digestive; ear; endocrine and metabolic; eye; genitourinary; heart

and circulatory; infectious and parasitic; mental disorders; musculoskeletal; neoplastic; nervous; respiratory; skin; and any other structure. Further details are reported elsewhere.[12 13]

Statistical analysis

All statistical analyses were conducted using Stata/IC V14.0 (Stata Corporation, College Station, Texas, USA) and controlled for the complex survey strategy employed in the 2008 HSE (primary sampling units, clustering and survey weights) in order to produce estimates representing the national population.[12 13]

Covariate selection and missing data

Multiple linear regression models were used to assess the associations between measures of total accumulated MVPA time and BMI with HbA1c after the adjustment for confounders. Confounders were considered for inclusion as follows: primarily using all the available data, in separate models for MVPA and BMI with HbA1c as the dependent variable, confounders were included based on the criteria of changing the regression coefficient for either MVPA or BMI by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time.[17] The confounders examined included: income, socioeconomic status, disease index, any prescribed medication, smoking status, reported fruit and vegetable consumption, light-intensity physical activity time and sedentary time. Of these, only income and any prescribed medication affected the relationships of MVPA and BMI with HbA1c (see online supplementary materials - Table S1), and were therefore included as confounders in all analyses. A complete-case analysis was used for handling any missing data (BMI (n=185), HbA1c (n = 746) and covariate: income (n

= 334)). In total 1,109 adults provided valid accelerometer data with complete BMI, HbA1c and covariate (age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time) data and were included for analysis (see online supplementary materials - Figure S1). Participant characteristics of the included sample (n = 1,109) were tabulated. Categorical variables were presented as numbers and proportions, whereas continuous variables were summarised as means and standard deviations.

Continuous measures of MVPA and BMI

Model 1 examined the associations between continuous measures of total accumulated MVPA time (presented as 30 minutes/day increments) or BMI (presented as of 1 kg/m^2 increments) with HbA1c, and adjusted for: age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time. Model 2 further adjusted for BMI (for MVPA analysis) and MVPA (for BMI analysis). Interaction analyses investigated if results for MVPA and BMI were modified by sex (significant results, if any, were stratified by men and women) and age (significant results, if any, were stratified at 60 years of age), and whether the association of MVPA with HbA1c was modified by BMI or vice-versa (significant results, if any, were stratified at 150 minutes/week of MVPA; and at a BMI threshold of 30.0 kg/m^2).

Mutually exclusive categories of MVPA and BMI

For descriptive purposes and to investigate the separate and combined associations of physical activity and obesity, a multiple linear regression model was fitted to analyse the differences in HbA1c between mutually exclusive categories of total accumulated MVPA time and BMI. To mirror national and international guidance,[18 19]

MVPA status was classified as 'physically active' or 'physically inactive' on the basis of whether or not participants accumulated a total of ≥150 minutes/week of MVPA, respectively. BMI status was determined as 'non-obese' or 'obese' on the basis of a BMI threshold of 30.0 kg/m^2 (i.e. non-obese if BMI <30.0 kg/m^2 and obese if BMI ≥30.0 kg/m^2). These categories allowed four mutually exclusive groups: (1) 'physically active & non-obese', (2) 'physically active & obese', (3) 'physically inactive & non-obese', and (4) 'physically inactive & obese'. The weighted prevalence (n (%)) and characteristics of the participants in each category were computed and tabulated. The 'physically inactive and obese' category was selected as the reference group as it was hypothesised *a priori* to be the least desirable state. The model adjusted for all the covariates stated previously (i.e. age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time).

All reported p-values were two-sided, and in order to account for multiple comparisons, p<0.01 was considered to be statistically significant for all analyses. Results for the regression analyses are presented as mean differences (99% confidence intervals) in HbA1c.

Sensitivity analysis

In order to examine the robustness of the reported associations, the following sensitivity analyses were conducted: (1) BMI was replaced with waist circumference (presented as 1 cm increments) in all described investigations with mutually exclusive categorical data defined as 'obese' (≥102 cm for men and ≥88 cm for women) or 'non-obese' (<102 cm for men and <88 cm for women); (2) 'Obese' was defined as having a BMI of ≥27.5 kg/m^2 for the mutually exclusive categorical data;

and (3) Participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes for the mutually exclusive categorical data.

RESULTS

Participant characteristics

Table 1 displays the characteristics of the included 1,109 participants [mean age (standard deviation (SD)) = 51.0 (16.5) years; mean BMI (SD) = 27.3 (4.8) kg/m^2; mean total accumulated MVPA time (SD) = 30.8 (25.8) minutes] across the derived mutually exclusive categories of MVPA and BMI.

Associations of physical activity and body mass index with glycated haemoglobin

Table 1 - Participant characteristics

Characteristic		Sample	'Physically active & non-obese'	'Physically active & obese'	'Physically inactive & non-obese'	'Physically inactive & obese'
		N = 1,109	n = 493; 45.9%	n = 118; 10.7%	n = 343; 29.9%	n = 155; 13.5%
Age (years) †		51.0 (16.5)	46.0 (14.7)	51.1 (13.2)	55.2 (18.4)	58.4 (15.0)
Body Mass Index (kg/m^2) †		27.3 (4.8)	25.1 (2.7)	33.4 (3.0)	25.5 (3.2)	34.3 (3.9)
By Sex:	Men	27.6 (4.2)	25.4 (2.6)	33.3 (2.5)	26.3 (2.6)	34.2 (3.1)
	Women	27.0 (5.4)	24.6 (2.9)	33.5 (3.6)	24.8 (3.4)	34.4 (4.4)
Waist Circumference (cm) †		92.9 (13.9)	87.3 (10.5)	106.9 (9.5)	89.6 (12.2)	109.1 (11.3)
By Sex:	Men	98.4 (12.1)	92.2 (9.0)	112.0 (7.6)	97.6 (9.4)	114.1 (9.0)
	Women	87.2 (13.5)	81.1 (8.9)	101.2 (7.9)	83.3 (10.1)	104.8 (11.4)
Ethnicity ‡						
White		1,055 (94.2)	470 (94.7)	112 (94.3)	324 (93.4)	149 (94.7)
Non-White		54 (5.8)	23 (5.3)	6 (5.7)	19 (6.6)	6 (5.3)
Income ‡						
Low		287 (24.0)	92 (16.7)	31 (24.3)	111 (30.6)	53 (33.5)
Intermediate		364 (33.5)	159 (32.9)	43 (38.5)	107 (32.0)	55 (35.6)
High		458 (42.5)	242 (50.4)	44 (37.2)	125 (37.4)	47 (30.9)
Sex ‡						
Men		523 (50.2)	257 (55.4)	60 (53.5)	142 (43.5)	64 (45.0)
Women		586 (49.8)	236 (44.6)	58 (46.5)	201 (56.5)	91 (55.0)

Any Prescribed Medication ‡					
No	503 (47.7)	278 (58.0)	57 (49.3)	129 (40.1)	39 (28.5)
Yes	606 (52.3)	215 (42.0)	61 (50.7)	214 (59.9)	116 (71.5)
Accelerometer Wear-Time † (no. of minutes/valid day)	867.7 (72.1)	873.2 (68.9)	870.4 (77.1)	854.9 (74.7)	875.1 (69.3)
Total Accumulated Moderate-to-Vigorous-Intensity Physical Activity Time † (no. of minutes/valid day)	30.8 (25.8)	47.2 (25.5)	41.3 (18.6)	11.5 (6.4)	9.7 (5.9)
Moderate-to-Vigorous-Intensity Physical Activity Time in Bouts of ≥10 Minutes † (no. of minutes/valid day)	10.8 (16.2)	39.8 (22.0)	36.4 (11.7)	5.6 (6.1)	4.5 (5.8)
Number of Valid Days ‡					
4	46 (4.5)	17 (3.9)	9 (8.0)	12 (3.5)	8 (6.1)
5	80 (7.5)	32 (6.7)	5 (4.3)	31 (9.3)	12 (8.5)
6	209 (19.7)	89 (18.4)	20 (18.0)	77 (24.1)	23 (15.8)
7	774 (68.3)	355 (71.0)	84 (69.7)	223 (63.1)	112 (69.6)
Glycated Haemoglobin (HbA1c)					
[mmol/mol] †	38.1 (7.3)	36.1 (4.9)	38.5 (4.8)	39.2 (9.2)	41.9 (8.7)
[%] †	5.63 (0.67)	5.45 (0.45)	5.67 (0.44)	5.74 (0.84)	5.98 (0.79)

All analyses controlled for primary sampling units, clustering and survey weights.

† *Continuous variable; Mean (Standard Deviation)*

‡ *Categorical variable; n (Proportion (%))*

Continuous measures of MVPA and BMI

Table 2 displays the associations between continuous measures of total accumulated MVPA time, BMI and HbA1c. In the maximally adjusted model, every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.07% ($p<0.001$)] lower HbA1c level. Each 1 kg/m^2 increment in BMI was associated with a

0.2 mmol/mol [0.02% (p<0.001)] higher HbA1c level. Results were not modified by age (p=0.104 for age x MVPA interaction; p=0.300 for age x BMI interaction) or sex (p=0.975 for sex x MVPA interaction; p=0.170 for sex x BMI interaction). However, the MVPA x BMI interaction term was significant (p=0.004). Table 3 displays the associations of MVPA with HbA1c stratified by BMI status, and the associations of BMI with HbA1c stratified by MVPA status. The association of MVPA with HbA1c was stronger in obese individuals, where every 30 minutes/day increment in MVPA was associated with a 1.5 mmol/mol [0.13% (p<0.001)] lower HbA1c level. In non-obese individuals, every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.06% (p<0.001)] lower HbA1c level. In contrast, the association of BMI with HbA1c remained stable across MVPA categories.

Associations of physical activity and body mass index with glycated haemoglobin

Table 2 - Adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and body mass index (BMI) with glycated haemoglobin (HbA1c)

Adjusted linear regression model	HbA1c (dual units)	MVPA (30 minutes/day)		BMI (1 kg/m^2)	
		Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
Model 1	[mmol/mol] [%]	**-0.9 (-1.4, -0.4)** **-0.08 (-0.13, -0.04)**	**<0.001**	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**
Model 2	[mmol/mol] [%]	**-0.7 (-1.2, -0.2)** **-0.07 (-0.11, -0.02)**	**<0.001**	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**

*All analyses controlled for primary sampling units, clustering and survey weights. **Bold** indicates statistical significance at p<0.01. Model 1 adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time. Model 2 additionally adjusted for BMI (for MVPA analysis) and MVPA (for BMI analysis).*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m^2 increment in BMI*

Associations of physical activity and body mass index with glycated haemoglobin

Table 3 - Interaction analysis: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and body mass index (BMI) with glycated haemoglobin (HbA1c) stratified by MVPA and BMI levels

P-value of MVPA x BMI interaction term	Stratification	HbA1c (dual units)	MVPA (30 minutes/day) Beta (99% CI) †	MVPA (30 minutes/day) p-value	BMI (1 kg/m^2) Beta (99% CI) ‡	BMI (1 kg/m^2) p-value
0.004	BMI <30.0 kg/m^2	[mmol/mol] [%]	**-0.7 (-1.2, -0.1)** **-0.06 (-0.11, -0.01)**	**0.002**	-	-
	BMI ≥30.0 kg/m^2	[mmol/mol] [%]	**-1.5 (-2.3, -0.6)** **-0.13 (-0.21, -0.05)**	**<0.001**	-	-
	MVPA <150 mins/week	[mmol/mol] [%]	-	-	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**
	MVPA ≥150 mins/week	[mmol/mol] [%]	-	-	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**

All analyses controlled for primary sampling units, clustering and survey weights. ***Bold*** *indicates statistical significance at p<0.01. Models adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

Associations of physical activity and body mass index with glycated haemoglobin

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m^2 increment in BMI*

Mutually exclusive categories of MVPA and BMI

Table 4 shows the differences in HbA1c levels between mutually exclusive categories of total accumulated MVPA time and BMI. Compared with individuals who were 'physically inactive & obese', those who were 'physically active & obese' or 'physically active & non-obese' had significantly lower HbA1c levels by 2.1 mmol/mol [0.19% (p=0.005)] and 3.5 mmol/mol [0.32% (p<0.001)], respectively. However, average HbA1c levels were not significantly different between the 'physically inactive & non-obese' and 'physically inactive and obese' categories.

Associations of physical activity and body mass index with glycated haemoglobin

Table 4 - Adjusted linear regression model showing the associations between mutually exclusive categories of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and body mass index (BMI) with glycated haemoglobin (HbA1c)

HbA1c (dual units)	'Physically active & non-obese'		'Physically active & obese'		'Physically inactive & non-obese'		'Physically inactive & obese'
	Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	
[mmol/mol] [%]	**-3.5 (-5.2, -1.9)** **-0.32 (-0.47, -0.18)**	**<0.001**	**-2.1 (-4.1, -0.2)** **-0.19 (-0.37, -0.02)**	**0.005**	-1.9 (-3.8, 0.0) -0.17 (-0.35, 0.00)	0.012	Reference

All analyses controlled for primary sampling units, clustering and survey weights.

'Physically active' was defined as: ≥150 minutes/week of total accumulated MVPA.

'Physically inactive' was defined as: <150 minutes/week of total accumulated MVPA.

'Obese' was defined as: BMI ≥30.0 kg/m^2.

'Non-obese' was defined as: BMI <30.0 kg/m^2.

***Bold** indicates statistical significance at p<0.01. Model adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) in comparison to the 'physically inactive and obese' category*

Sensitivity analysis

Sensitivity analyses indicated robustness. When waist circumference was used in place of BMI, the pattern of results was unchanged (see online supplementary materials - Table S2). The results were not modified by age (p=0.069 for age x MVPA interaction; p=0.922 for age x waist circumference interaction) or sex (p=0.923 for sex x MVPA interaction; p=0.483 for sex x waist circumference interaction). However, the pattern of results was exaggerated for the MVPA x waist circumference interaction analysis (p<0.001 for interaction; see online supplementary materials - Table S3). In those with high waist circumference, every 30 minutes/day increment in MVPA was associated with a 1.8 mmol/mol [0.16% (p<0.001)] lower HbA1c level. The other sensitivity analyses also indicated stability; although the prevalence in each category varied across the different methods used (see online supplementary materials - Table S4), the key findings were largely unaffected (see online supplementary materials - Table S5).

DISCUSSION

This study quantified the independent and combined associations of objectively measured MVPA and BMI with HbA1c in a sample of English adults. Both MVPA and BMI were independently associated with HbA1c; every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.07%] lower HbA1c level and each 1 kg/m^2 increment in BMI was associated with a 0.2 mmol/mol [0.02%] higher HbA1c level. Results for MVPA were modified by BMI status, with a stronger association seen in obese individuals. For those with a BMI of 30.0 kg/m^2 or higher, every 30 minutes/day increment in MVPA was associated with a 1.5 mmol/mol [0.13%] lower

HbA1c level. Compared to individuals categorised as 'physically inactive & obese', only those categorised as 'physically active & obese' or 'physically active & non-obese' had lower HbA1c levels by 2.1 mmol/mol [0.19%] and 3.5 mmol/mol [0.32%], respectively.

Strengths and limitations

Our study has several strengths, which include: the use of HbA1c, a validated and clinically employed measure of glycaemic status; a well-characterised national survey which employs a multifaceted stratified random sampling procedure; examining age and sex interactions; and a range of sensitivity analyses. The key limitation resides in the cross-sectional design which eliminates the possibility of establishing causality. In addition, although we adjusted for a wide range of important lifestyle, demographic and clinical variables, it is possible that unmeasured factors were confounding the reported associations. Generalizability could also be limited by the amount of missing biochemical and covariate data, as well as the small fraction of participants who were asked to wear an accelerometer. However, the key demographics (age, BMI, sex) of the included sample in this study were similar to the full 2008 HSE adult cohort.[20] Even though HbA1c is an established clinical measure of glycaemia that reflects average glucose concentrations over the previous 2-3 months, it is not a perfect index of blood glucose for all individuals, and it does not adequately reflect the glycaemic control status in some diseases that change the life span of erythrocytes, such as chronic liver disease.[21] In addition, although the inclusion of objectively measured MVPA is a notable strength, the device used also has some limitations. Reliance on vertical accelerations to quantify movement and lack of waterproofing means that some activities like cycling may not have been

adequately captured whereas others like swimming were not captured at all. However, ambulation, which makes up the vast majority of human movement, is accurately assessed by accelerometers. Furthermore, cycling and swimming can be considered to be atypical activities in this cohort; with only a small proportion of participants reporting any cycling or swimming activities at all.[12]

Other studies

Our findings extend previous research using HSE data which have reported an association between MVPA and HbA1c in a subsample of older adults.[22] The study also found that neither self-reported or accelerometer assessed sedentary time was associated with HbA1c. Others have also reported a lack of association between sedentary time and HbA1c in HSE using both objective and self-reported data.[23] However, previous studies using HSE did not examine the independent association or modifying effect of BMI. This contrasts with the strong and consistent association reported in the present study for MVPA, suggesting that MVPA may be the stronger determinant of HbA1c in HSE. Our findings are also are consistent with analyses of NHANES which have shown that there was no statistical difference in HbA1c between active obese adults and inactive normal weight adults, with a further analysis showing that an association between MVPA and HbA1c was only present in those with a moderate or high risk of type 2 diabetes;[24 25] however, neither of these studies formally tested for an interaction with BMI. By showing the association of MVPA with HbA1c is stronger in obese adults, our results suggest that MVPA may have greater potential to moderate glycaemic status at higher levels of BMI and confirms previous research suggesting that active obese adults have healthier levels of HbA1c than inactive obese adults. The difference in HbA1c across the mutually

exclusive categories and for every 30 minutes/day increment in MVPA observed for obese individuals in our study is likely to be clinically meaningful beyond diabetes risk. For example, in adults without diabetes, each 0.1% unit increment in HbA1c has been associated with a 2% higher risk of mortality and a 4% higher risk of coronary heart disease or stroke.[26]

Interpretations

Our finding that MVPA may be metabolically protective in obese individuals is also consistent with studies that have shown that cardiorespiratory fitness, which is partly moderated by MVPA, is also an important determinant of metabolic health in obesity.[11] Other studies have consistently reported that obese individuals with moderate to high fitness have a lower risk of all-cause and cardiovascular mortality those with normal BMI but low fitness.[27] However, the extent to which MVPA and fitness can reduce the excess risks of obesity remains controversial,[28] supporting the need for further research in this area. Our results are supported by intervention studies and known mechanistic pathways linking reduced adiposity and higher physical activity to better glucose control and reduced insulin resistance.[3 29-32] The impact of physical activity on glucose levels and insulin resistance in obesity may also be enhanced by preferentially shifting the storage of excess fat away from metabolically active sites, such as within visceral compartments or organs, without effecting overall level adiposity.[33]

Whilst intervention studies have established and quantified the effects on HbA1c levels following interventions aimed at increasing physical activity or reducing body weight in individuals with T2DM,[7-9] the associations between these factors in the

general population are less clear. This is an important limitation as diabetes prevention recommendations and programmes within routine care are increasingly moving towards identifying and referring individuals on the basis of HbA1c whilst also evaluating effectiveness through changes to HbA1c.[4-6] The latter point is particularly important as there is a lack of data supporting the magnitude of potential differences in HbA1c anticipated with specific differences in health behaviours.

Conclusions

In conclusion, this study quantifies the association between MVPA, BMI and HbA1c and shows that the association of MVPA with HbA1c is stronger in those with higher BMI levels. Finding ways of translating this information into encouraging obese people to increase their physical activity levels as an intervention for lowering HbA1c might be important to improve public health and allow for more personalised educational and lifestyle interventions to be implemented. However, given the limitations which preclude inferences of causality, these conclusions need to be confirmed by interrogating data from completed diabetes prevention trials or through further experimental studies.

DECLARATIONS

Ethics approval and consent to participate

Ethical approval for the 2008 Health Survey for England study was obtained from the Oxford A Research Ethics Committee (reference number: 07/H0604/102). Participants provided written informed consent.

Data sharing statement

Permission to use the 2008 Health Survey for England accelerometer data files can be obtained from the National Centre for Social Research (NatCen) (http://www.natcen.ac.uk/). All other data are openly available to download from the UK Data Archive (https://discover.ukdataservice.ac.uk/series/?sn=2000021).

Competing interests

SJHB: Funding has been received since 2012 for consultancy work from Fitness First, Nuffield Health, Unilever, and Weight Watchers, and for travel from The Coca Cola Foundation. None of these are currently active. Funding was received in 2016 for consultancy work for Halpern Limited. A sit-to-stand desk was kindly provided by Ergotron from 2012-2014. Advice has been requested by and offered to Active Working and Get Britain Standing. TY, MJD and KK: Developed a prevention programme, Let's Prevent Diabetes, selected to be part of Healthier You: The NHS Diabetes Prevention Programme in collaboration with Ingeus UK Limited. KK also chaired NICE guidance for the prevention of type 2 diabetes mellitus (PH 38), with TY and MJD part of the committee. All other authors declare that they have no competing interests.

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Authors' contributions

TY had the original idea for the analysis, which was further developed and refined by KB, CLE, DHB, DWE, JMRG, AK, LV, AJS, NS, SJHB, MH, MJD and KK. CLE processed the 2008 Health Survey for England accelerometer data. KB carried out the statistical analysis and worked with TY to write the first and revised drafts of the manuscript. KB, TY, CLE, DHB, DWE, JMRG, AK, LV, AJS, NS, SJHB, MH, MJD and KK edited and reviewed the manuscript drafts. KB, TY, CLE, DHB, DWE, JMRG, AK, LV, AJS, NS, SJHB, MH, MJD and KK approved the final version of the manuscript.

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Research Unit (NIHR DLPA BRU) based at University Hospitals of Leicester and Loughborough University, the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC – EM) and the Leicester Clinical Trials Unit (LCTU). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health (DoH).

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SUPPLEMENTARY MATERIALS

Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin within the general population: a cross-sectional analysis of the 2008 Health Survey for England

Authors: Kishan Bakrania*, Thomas Yates*, Charlotte L. Edwardson, Danielle H. Bodicoat, Dale W. Esliger, Jason M.R. Gill, Aadil Kazi [2, 3], Latha Velayudhan, Alan J. Sinclair, Naveed Sattar, Stuart J.H. Biddle, Mark Hamer, Melanie J. Davies and Kamlesh Khunti

* = joint first authors

Corresponding author: Dr. Charlotte L. Edwardson, Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, Leicestershire, LE5 4PW, United Kingdom. Phone: +44(0)116 258 8577. Email: ce95@le.ac.uk.

Number of supplementary figures: 1

Figure S1 - Flow chart of study participants

Number of supplementary tables: 5

Table S1 - Confounder analysis based on the criteria of changing the regression coefficient for either total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time or body mass index (BMI) by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time

Table S2 - Sensitivity analyses: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c)

Table S3 - Sensitivity analyses: interaction analysis: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c) stratified by MVPA and waist circumference levels

Table S4 - Sensitivity analyses: weighted mutually exclusive category prevalence

Table S5 - Sensitivity analyses: adjusted linear regression models showing the associations between mutually exclusive categories of moderate-to-vigorous-intensity physical activity (MVPA) time and obesity status with glycated haemoglobin (HbA1c)

Figure S1 - Flow chart of study participants

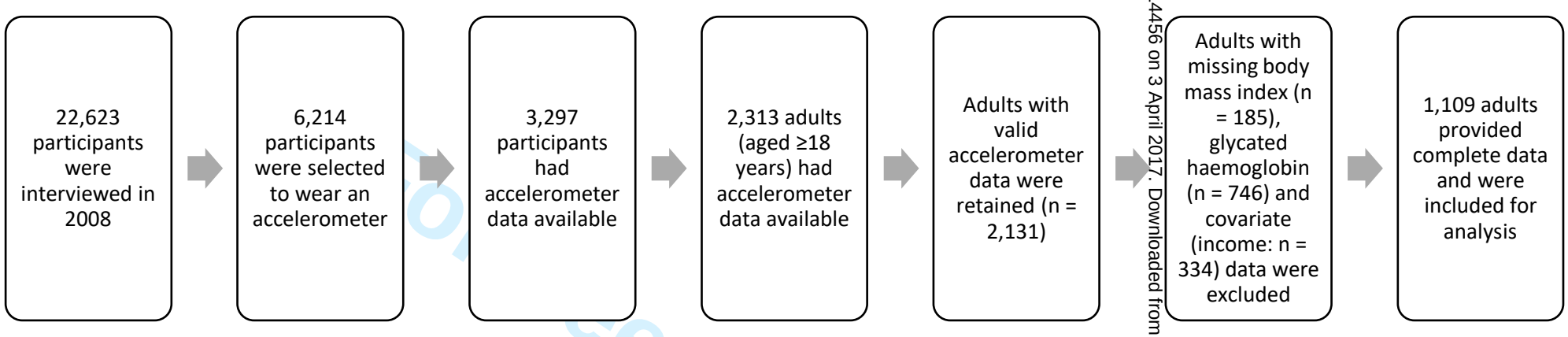

Table S1 - Confounder analysis based on a criteria of changing the regression coefficient for either total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time or body mass index (BMI) by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time

		MVPA (30 minutes/day): Beta †	% Change in MVPA Beta	BMI (1 kg/m^2): Beta ‡	% Change in BMI Beta
HbA1c (dual units)	[mmol/mol]	-1.08619	-	0.27118	-
	[%]	-0.09939		0.02481	
Covariate individually added to basic model (age, sex, ethnicity and accelerometer wear-time)					
Disease index		-1.00775 -0.09221	7.2	0.26435 0.02419	-2.5
Reported fruit & vegetable consumption		-1.09698 -0.10037	-1.0	0.26803 0.02452	-1.2
Income		-1.06915 -0.09783	1.6	**0.23041** **0.02108**	**-15.0**
Smoking status		-1.05337 -0.09638	3.0	0.28741 0.02630	6.0
Socioeconomic status		-1.15279 -0.10548	-6.1	0.26994 0.02470	-0.5
Any prescribed medication		**-0.97137** **-0.08888**	**10.6**	0.25501 0.02343	-5.6

Sedentary time	-1.18817 -0.10872	-9.4	0.27613 0.02472	-0.4
Light-intensity physical activity time	-1.11946 -0.10243	-3.1	0.27152 0.02484	0.1

All analyses controlled for primary sampling units, clustering and survey weights. Confounders were considered for inclusion as follows: primarily using all the available data, in separate models for MVPA and BMI with glycated haemoglobin (HbA1c) as the dependent variable, confounders were included based on a criteria of changing the regression coefficient for either MVPA or BMI by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex, and accelerometer wear-time. ***Bold*** *indicates a ≥10% change in the regression coefficient for either MVPA or BMI.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m^2 increment in BMI*

Table S2 - Sensitivity analyses: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c)

Adjusted linear regression model	HbA1c (dual units)	MVPA (30 minutes/day)		Waist Circumference (1 cm)	
		Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
Model 1	[mmol/mol] [%]	**-0.9 (-1.4, -0.4)** **-0.08 (-0.13, -0.03)**	**<0.001**	**0.1 (0.1, 0.1)** **0.01 (0.01, 0.01)**	**<0.001**
Model 2	[mmol/mol] [%]	**-0.6 (-1.0, -0.1)** **-0.05 (-0.10, -0.01)**	**0.003**	**0.1 (0.1, 0.1)** **0.01 (0.01, 0.01)**	**<0.001**

*All analyses controlled for primary sampling units, clustering and survey weights. **Bold** indicates statistical significance at p<0.01. Model 1 adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time. Model 2 additionally adjusted for waist circumference (for MVPA analysis) and MVPA (for waist circumference analysis).*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 cm increment in waist circumference*

Table S3 - Sensitivity analyses: interaction analysis: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c) stratified by MVPA and waist circumference levels

P-value of MVPA x Waist Circumference interaction term	Stratification	HbA1c (dual units)	MVPA (30 minutes/day)		Waist Circumference (1 cm)	
			Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
<0.001	Low Waist Circumference	[mmol/mol] [%]	-0.3 (-0.7, 0.0) -0.03 (-0.06, 0.00)	0.024	-	-
	High Waist Circumference	[mmol/mol] [%]	**-1.8 (-3.0, -0.5)** **-0.16 (-0.28, -0.05)**	**<0.001**	-	-
	MVPA <150 mins/week	[mmol/mol] [%]	-	-	**0.1 (0.1, 0.2)** **0.01 (0.01, 0.02)**	**<0.001**
	MVPA ≥150 mins/week	[mmol/mol] [%]	-	-	**0.1 (0.0, 1)** **0.01 (0.00, 0.01)**	**<0.001**

All analyses controlled for primary sampling units, clustering and survey weights. 'High Waist Circumference' was defined as having a waist circumference of ≥102 cm for men and ≥88 cm for women. ***Bold*** *indicates statistical significance at p<0.01. Models adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 cm increment in waist circumference*

Table S4 - Sensitivity analyses: weighted mutually exclusive category prevalence

	Weighted Prevalence [%]			
Method	'Physically active & non-obese'	'Physically active & obese'	'Physically inactive & non-obese'	'Physically inactive & obese'
Reference	45.9%	10.7%	29.9%	13.5%
1	37.8%	19.0%	20.0%	23.2%
2	36.1%	20.5%	20.7%	22.7%
3	14.3%	1.8%	61.5%	22.4%

All analyses controlled for primary sampling units, clustering and survey weights.

Reference Method = Mutually exclusive categories derived and utilised in the main analysis

Method 1 = 'Obese' was defined as having a waist circumference of ≥102 cm for men and ≥88 cm for women

Method 2 = 'Obese' was defined as having a body mass index of ≥27.5 kg/m^2

Method 3 = Participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes

Table S5 - Sensitivity analyses: adjusted linear regression models showing the associations between mutually exclusive categories of moderate-to-vigorous-intensity physical activity (MVPA) time and obesity status with glycated haemoglobin (HbA1c)

Method	HbA1c (dual units)	'Physically active & non-obese'		'Physically active & obese'		'Physically inactive & non-obese'		'Physically inactive & obese'
		Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	
Reference	[mmol/mol] [%]	**-3.5 (-5.2, -1.9)** **-0.32 (-0.47, -0.18)**	**<0.001**	**-2.1 (-4.1, -0.2)** **-0.19 (-0.37, -0.02)**	**0.005**	-1.9 (-3.8, 0.0) -0.17 (-0.35, 0.00)	0.012	Reference
1	[mmol/mol] [%]	**-4.1 (-5.9, -2.2)** **-0.37 (-0.54, -0.21)**	**<0.001**	**-2.5 (-4.4, -0.6)** **-0.23 (-0.40, -0.05)**	**0.001**	**-3.1 (-5.0, -1.2)** **-0.29 (-0.46, -0.11)**	**<0.001**	Reference
2	[mmol/mol] [%]	**-2.9 (-4.1, -1.7)** **-0.27 (-0.38, -0.16)**	**<0.001**	**-1.5 (-2.9, -0.2)** **-0.14 (-0.27, -0.02)**	**0.004**	-0.9 (-2.9, 1.1) -0.08 (-0.27, 0.01)	0.229	Reference
3	[mmol/mol] [%]	**-3.4 (-4.7, -2.1)** **-0.31 (-0.43, -0.20)**	**<0.001**	-2.0 (-4.3, 0.3) -0.18 (-0.39, 0.03)	0.027	**-1.7 (-3.0, -0.4)** **-0.16 (-0.28, -0.04)**	**0.001**	Reference

All analyses controlled for primary sampling units, clustering and survey weights.

Reference Method = Mutually exclusive categories derived and utilised in the main analysis

Method 1 = 'Obese' was defined as having a waist circumference of ≥102 cm for men and ≥88 cm for women

Method 2 = 'Obese' was defined as having a body mass index of ≥27.5 kg/m^2

Method 3 = Participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes

***Bold** indicates statistical significance at p<0.01. Models adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) in comparison to the 'physically inactive and obese' category*

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Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin within the general population: a cross-sectional analysis of the 2008 Health Survey for England

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Complete List of Authors:	Bakrania, Kishan; University of Leicester Diabetes Research Centre Yates, Thomas; University of Leicester, Diabetes Reseach Centre Edwardson, Charlotte; University of Leicester, Bodicoat, Danielle; University of Leicester, Esliger, Dale; Loughborough University, Sport, Exercise and Health Sciences; NIHR, Diet Lifestyle and Physical Activity Biomedical Research Unit Gill, Jason; University of Glasgow, Institute of Cardiovascular and Medical Sciences Kazi, Aadil; University of Leicester Diabetes Research Centre Velayudhan , Latha ; University of Leicester Sinclair, Alan; Aston University Sattar, Naveed; University of Glasgow, BHF centre Biddle, Stuart; Victoria University Hamer, Mark; Loughborough University, Sport, Exercise and Health Sciences Davies, Melanie; University of Leicester Diabetes Research Centre Khunti, Kamlesh; University of Leicester Diabetes Research Centre
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Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin within the general population: a cross-sectional analysis of the 2008 Health Survey for England

Authors: Kishan Bakrania* [1, 2, 3, 4], Thomas Yates* [2, 3], Charlotte L. Edwardson [2, 3], Danielle H. Bodicoat [2, 4], Dale W. Esliger [3, 5], Jason M.R. Gill [6], Aadil Kazi [2, 3], Latha Velayudhan [7, 8], Alan J. Sinclair [9], Naveed Sattar [6], Stuart J.H. Biddle [10], Mark Hamer [3, 5], Melanie J. Davies [2, 3] and Kamlesh Khunti [2, 4]

* = joint first authors

[1] Department of Health Sciences, University of Leicester, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[2] Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[3] National Institute for Health Research (NIHR) Leicester-Loughborough Diet, Lifestyle and Physical Activity Biomedical Research Unit (BRU), Diabetes Research Centre, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

[4] National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care – East Midlands (CLAHRC – EM), Diabetes Research Centre, Leicester General Hospital, Leicester, Leicestershire, LE5 4PW, United Kingdom.

Associations of physical activity and body mass index with glycated haemoglobin

[5] School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, Leicestershire, LE11 3TU, United Kingdom.

[6] British Heart Foundation Glasgow Cardiovascular Research Centre (BHF GCRC), Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, G12 8TA, United Kingdom.

[7] Psychiatry for the Elderly, Department of Health Sciences, University of Leicester, Leicester, Leicestershire, LE1 7RH, United Kingdom.

[8] Older People's Mental Health, Oxleas National Health Service (NHS) Foundation Trust, Bridgeways, Bromley, BR8 2JA, United Kingdom.

[9] Diabetes Frail Ltd, Aston University, Birmingham, West Midlands, B4 7ET, United Kingdom.

[10] Institute of Sport, Exercise & Active Living, Victoria University, Melbourne, VIC 8001, Australia.

Corresponding author: Dr. Charlotte L. Edwardson, Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, Leicestershire, LE5 4PW, United Kingdom. Phone: +44(0)116 258 8577. Email: ce95@le.ac.uk.

Author email addresses: Kishan Bakrania (kb318@le.ac.uk), Thomas Yates (ty20@le.ac.uk), Charlotte L. Edwardson (ce95@le.ac.uk), Danielle H. Bodicoat (dhm6@le.ac.uk), Dale W. Esliger (D.Esliger@lboro.ac.uk), Jason M.R. Gill (Jason.Gill@glasgow.ac.uk), Aadil Kazi (Aadil.Kazi@uhl-tr.nhs.uk), Latha Velayudhan (lv24@le.ac.uk), Alan J. Sinclair (sinclair.5@btinternet.com), Naveed Sattar (Naveed.Sattar@glasgow.ac.uk), Stuart J.H. Biddle

(Stuart.Biddle@vu.edu.au), Mark Hamer (M.Hamer@lboro.ac.uk), Melanie J. Davies (melanie.davies@uhl-tr.nhs.uk) and Kamlesh Khunti (kk22@le.ac.uk).

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ABSTRACT

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Objectives: To investigate the associations of objectively measured moderate-to-vigorous-intensity physical activity (MVPA) and body mass index (BMI) with glycated haemoglobin (HbA1c) in a national sample of English adults.

Methods: The 2008 Health Survey for England data were used with 1,109 participants aged ≥18 years providing complete data. MVPA time was assessed using an accelerometer. Weighted linear regression models, adjusted for several confounders, quantified the associations between continuous measures of MVPA and BMI with HbA1c. Interaction analyses were implemented to observe whether the association of MVPA with HbA1c was modified by BMI or vice versa. Further weighted linear regression models examined the differences in HbA1c across four mutually exclusive categories of MVPA and BMI: (1) 'physically active & non-obese', (2) 'physically active & obese', (3) 'physically inactive & non-obese', and (4) 'physically inactive & obese'. 'Physically active' was defined as: ≥150 minutes/week of MVPA. 'Obese' was defined as: BMI ≥30.0 kg/m^2. A wide range of sensitivity analyses were also implemented.

Results: Every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.07% (p<0.001)] lower HbA1c level. Each 1 kg/m^2 increment in BMI was associated with a 0.2 mmol/mol [0.02% (p<0.001)] higher HbA1c level. The association of MVPA with HbA1c was stronger in obese individuals (-1.5 mmol/mol [-0.13% (p<0.001)]) than non-obese individuals (-0.7 mmol/mol [-0.06% (p<0.001)]); p=0.004 for interaction. The association of BMI with HbA1c remained stable across MVPA categories. Compared to individuals categorised as 'physically inactive &

obese', only those categorised as 'physically active & obese' or 'physically active & non-obese' had lower HbA1c levels by 2.1 mmol/mol [0.19% (p=0.005)] and 3.5 mmol/mol [0.32% (p<0.001)], respectively. Sensitivity analyses indicated robustness and stability.

Conclusions: This study emphasises the importance of physical activity as a determinant of HbA1c, and suggests that the associations may be stronger in obese adults.

Keywords: Type 2 Diabetes Mellitus; Glycated Haemoglobin; Body Mass Index; Obesity; Moderate-to-Vigorous-Intensity Physical Activity; Epidemiology

Abbreviations: Type 2 Diabetes Mellitus (T2DM); Glycated Haemoglobin (HbA1c); Moderate-to-Vigorous-Intensity Physical Activity (MVPA); Body Mass Index (BMI); Health Survey for England (HSE); National Health Service (NHS); Oral Glucose Tolerance Test (OGTT); Standard Deviation (SD)

ARTICLE SUMMARY

Strengths and limitations of this study

- This study utilises glycated haemoglobin (HbA1c) as an outcome, a validated and clinically employed measure of diabetes risk.
- An objective measure of physical activity is employed.
- The cross-sectional design eliminates the possibility of establishing causality.
- The sample used in this study may not be completely representative of the general population.

INTRODUCTION

Diabetes mellitus is one of the most prevalent and costly chronic conditions accounting for between 7-14% of health care funding globally.[1] This health care burden is projected to continue rising into the future.[2] Type 2 diabetes mellitus (T2DM), the most common form of the condition, is consequently recognised as a health care priority. Given T2DM is predominantly a lifestyle-related chronic condition and that lifestyle interventions have consistently been shown to reduce the risk of T2DM across a range of diverse populations,[3] prevention strategies are largely focused on the promotion of healthy behaviours. In England, the National Health Service (NHS) has recently identified the prevention of T2DM as a leading priority and commissioned a national diabetes prevention programme based on behavioural counselling and lifestyle interventions that promote physical activity and weight loss in those at high risk.[4]

Revisions to the diagnostic criteria for T2DM in 2011 to include glycated haemoglobin (HbA1c),[5] an easy to assess and increasingly used measure of glycaemia that reflects average glucose concentrations over the previous 2-3 months, precipitated clinical changes more widely in the assessment of metabolic health.[4-6] However, whilst the effects of physical activity and weight loss on HbA1c are well-defined in populations with T2DM,[7-9] they are less clear in populations without diabetes.[10]

In this study, we use data from a national survey to quantify the associations of objectively measured moderate-to-vigorous-intensity physical activity (MVPA) and body mass index (BMI) with HbA1c in the general population, and observe whether

the association of MVPA with HbA1c is modified by BMI or vice versa. Here, we hypothesize that MVPA may provide a metabolically protective effect in obese individuals; since cardiorespiratory fitness, a factor that is partly moderated by MVPA, has previously been shown to be an important determinant of metabolic health in obesity.[11] We also examine the differences in HbA1c across mutually exclusive categories of MVPA and BMI.

METHODS

Study sample

The Health Survey for England (HSE) is a series of national annual surveys designed to examine the health and well-being of people living in England.[12 13] In order to obtain a population-based sample, these cross-sectional surveys employ a multistage stratified random sampling procedure. The 2008 HSE wave was centred on physical activity and fitness and included a subset of participants who were randomly selected to wear an accelerometer for the objective assessment of physical activity.[12 13] In total, accelerometer data on 2,313 adults (aged ≥18 years) were available, with 2,131 adults providing valid accelerometer data (see online supplementary materials - Figure S1). Participants provided written informed consent. Ethical approval for the 2008 HSE survey was obtained from the Oxford A Research Ethics Committee (reference number: 07/H0604/102). Further details are reported elsewhere.[12 13]

Physical activity

Physical activity and sedentary time were measured using an ActiGraph GT1M accelerometer (ActiGraph Corporation, Pensacola, Florida, USA) which was worn on the right hip for seven consecutive days during waking hours (except water-based activities).[12] The ActiGraph GT1M device was initialised to collect data using one minute epochs. Accelerometer files were processed using KineSoft V3.3.76 (KineSoft, Loughborough, UK). Accelerometer counts were used to calculate the total time spent in MVPA (≥1952 counts/minute), light-intensity physical activity (≥100 to <1952 counts/minute) and sedentary behaviour (<100 counts/minute).[14 15] Non-wear time was defined as any periods of continuous zero counts for ≥60 consecutive minutes.[16] Valid accelerometry data were defined as ≥10 hours of wear-time per day with ≥4 days of data. The average number of minutes per valid day spent in each intensity band were calculated.

Whilst time in total accumulated MVPA was used for the primary analysis, MVPA time accumulated in bouts of ≥10 minutes (allowing for a two minute exception in the intensity threshold) was also derived for a sensitivity analysis (see *Statistical analysis - Sensitivity analysis*).

BMI

A trained fieldworker recorded height (measured to the nearest 0.1 cm) and weight (measured to the nearest 0.1 kilogram using an electronic scale) readings.[13] BMI was calculated as the weight (in kilograms) divided by the square of the height (in metres).

Waist circumference

Waist circumference was defined as the midpoint between the lower rib and the upper boundary of the iliac crest. A nurse measured this twice to the nearest 0.1 cm using a tape and the average of the two readings was used.[13] This variable was included as differences in lean mass may exaggerate findings for physically active and obese individuals under the BMI measure. Therefore, sensitivity analyses replacing BMI with waist circumference were executed (see *Statistical analysis - Sensitivity analysis*).

HbA1c

Non-fasting blood samples were collected by a nurse for the analysis of HbA1c.[13] Blood analytes were assayed at the Royal Victoria Infirmary laboratory in Newcastle upon Tyne, England. Further details are reported elsewhere.[12 13] Data on HbA1c are reported in dual units: mmol/mol (to one decimal place) and % (to two decimal places).

Covariates

The following factors, collected by a trained fieldworker, were also utilised: age (in years); disease index (no diseases, one or more diseases); ethnicity (white, non-white); reported fruit and vegetable consumption (0, 1-3, 4-6, 7+ portions/day); income (low, intermediate, high); sex (men, women); smoking status (never smoked, ex-smoker, current smoker); socioeconomic status (national statistics socioeconomic classification: high, high-intermediate, intermediate, low intermediate, low); and any prescribed medication (no, yes). The 'disease index' variable was based on physician diagnosed conditions/illnesses relating to the following systems: blood and related organs; digestive; ear; endocrine and metabolic; eye; genitourinary; heart

and circulatory; infectious and parasitic; mental disorders; musculoskeletal; neoplastic; nervous; respiratory; skin; and any other structure. Further details are reported elsewhere.[12 13]

Statistical analysis

All statistical analyses were conducted using Stata/IC V14.0 (Stata Corporation, College Station, Texas, USA) and controlled for the complex survey strategy employed in the 2008 HSE (primary sampling units, clustering and survey weights) in order to produce estimates representing the national population.[12 13]

Covariate selection and missing data

Multiple linear regression models were used to assess the associations between measures of total accumulated MVPA time and BMI with HbA1c after the adjustment for confounders. Confounders were considered for inclusion as follows: primarily using all the available data, in separate models for MVPA and BMI with HbA1c as the dependent variable, confounders were included based on the criteria of changing the regression coefficient for either MVPA or BMI by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time.[17] The confounders examined included: income, socioeconomic status, disease index, any prescribed medication, smoking status, reported fruit and vegetable consumption, light-intensity physical activity time and sedentary time. Of these, only income and any prescribed medication affected the relationships of MVPA and BMI with HbA1c (see online supplementary materials - Table S1), and were therefore included as confounders in all analyses. A complete-case analysis was used for handling any missing data (BMI (n=185), HbA1c (n = 746) and covariate: income (n

= 334)). In total 1,109 adults provided valid accelerometer data with complete BMI, HbA1c and covariate (age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time) data and were included for analysis (see online supplementary materials - Figure S1). Participant characteristics of the included sample (n = 1,109) were tabulated. Categorical variables were presented as numbers and proportions, whereas continuous variables were summarised as means and standard deviations. As a supplementary analysis, we compared the basic characteristics (age, BMI, waist circumference, ethnicity, sex, total MVPA time, and MVPA time accumulated in bouts of ≥10 minutes) between the included and excluded participants from the sample of adults who provided valid accelerometer data; both groups were similar (see online supplementary materials - Table S2).

Continuous measures of MVPA and BMI

Model 1 examined the associations between continuous measures of total accumulated MVPA time (presented as 30 minutes/day increments) or BMI (presented as of 1 kg/m^2 increments) with HbA1c, and adjusted for: age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time. Model 2 further adjusted for BMI (for MVPA analysis) and MVPA (for BMI analysis). Interaction analyses investigated if results for MVPA and BMI were modified by sex (significant results, if any, were stratified by men and women) and age (significant results, if any, were stratified at 60 years of age), and whether the association of MVPA with HbA1c was modified by BMI or vice-versa (significant results, if any, were stratified at 150 minutes/week of MVPA; and at a BMI threshold of 30.0 kg/m^2).

Mutually exclusive categories of MVPA and BMI

For descriptive purposes and to investigate the separate and combined associations of physical activity and obesity, a multiple linear regression model was fitted to analyse the differences in HbA1c between mutually exclusive categories of total accumulated MVPA time and BMI. To mirror national and international guidance,[18 19] MVPA status was classified as 'physically active' or 'physically inactive' on the basis of whether or not participants accumulated a total of ≥150 minutes/week of MVPA, respectively. BMI status was determined as 'non-obese' or 'obese' on the basis of a BMI threshold of 30.0 kg/m^2 (i.e. non-obese if BMI <30.0 kg/m^2 and obese if BMI ≥30.0 kg/m^2). These categories allowed four mutually exclusive groups: (1) 'physically active & non-obese', (2) 'physically active & obese', (3) 'physically inactive & non-obese', and (4) 'physically inactive & obese'. The weighted prevalence (n (%)) and characteristics of the participants in each category were computed and tabulated. The 'physically inactive and obese' category was selected as the reference group as it was hypothesised *a priori* to be the least desirable state. The model adjusted for all the covariates stated previously (i.e. age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time).

All reported p-values were two-sided, and in order to account for multiple comparisons, p<0.01 was considered to be statistically significant for all analyses. Results for the regression analyses are presented as mean differences (99% confidence intervals) in HbA1c.

Sensitivity analysis

In order to examine the robustness of the reported associations, the following sensitivity analyses were conducted: (1) BMI was replaced with waist circumference

(presented as 1 cm increments) in all described investigations with mutually exclusive categorical data defined as 'obese' (≥102 cm for men and ≥88 cm for women) or 'non-obese' (<102 cm for men and <88 cm for women); (2) 'Obese' was defined as having a BMI of ≥27.5 kg/m^2 for the mutually exclusive categorical data; and (3) Participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes for the mutually exclusive categorical data.

RESULTS

Participant characteristics

Table 1 displays the characteristics of the included 1,109 participants [mean age (standard deviation (SD)) = 51.0 (16.5) years; mean BMI (SD) = 27.3 (4.8) kg/m^2; mean total accumulated MVPA time (SD) = 30.8 (25.8) minutes] across the derived mutually exclusive categories of MVPA and BMI.

Associations of physical activity and body mass index with glycated haemoglobin

346 *Table 1 - Participant characteristics*

Characteristic		Sample	'Physically active & non-obese'	'Physically active & obese'	'Physically inactive & non-obese'	'Physically inactive & obese'
		N = 1,109	n = 493; 45.9%	n = 118; 10.7%	n = 343; 29.9%	n = 155; 13.5%
Age (years) †		51.0 (16.5)	46.0 (14.7)	51.1 (13.2)	55.2 (18.4)	58.4 (15.0)
Body Mass Index (kg/m^2) †		27.3 (4.8)	25.1 (2.7)	33.4 (3.0)	25.5 (3.2)	34.3 (3.9)
By Sex:	Men	27.6 (4.2)	25.4 (2.6)	33.3 (2.5)	26.3 (2.6)	34.2 (3.1)
	Women	27.0 (5.4)	24.6 (2.9)	33.5 (3.6)	24.8 (3.4)	34.4 (4.4)
Waist Circumference (cm) †		92.9 (13.9)	87.3 (10.5)	106.9 (9.5)	89.6 (12.2)	109.1 (11.3)
By Sex:	Men	98.4 (12.1)	92.2 (9.0)	112.0 (7.6)	97.6 (9.4)	114.1 (9.0)
	Women	87.2 (13.5)	81.1 (8.9)	101.2 (7.9)	83.3 (10.1)	104.8 (11.4)
Ethnicity ‡						
White		1,055 (94.2)	470 (94.7)	112 (94.3)	324 (93.4)	149 (94.7)
Non-White		54 (5.8)	23 (5.3)	6 (5.7)	19 (6.6)	6 (5.3)
Income ‡						
Low		287 (24.0)	92 (16.7)	31 (24.3)	111 (30.6)	53 (33.5)
Intermediate		364 (33.5)	159 (32.9)	43 (38.5)	107 (32.0)	55 (35.6)
High		458 (42.5)	242 (50.4)	44 (37.2)	125 (37.4)	47 (30.9)
Sex ‡						
Men		523 (50.2)	257 (55.4)	60 (53.5)	142 (43.5)	64 (45.0)
Women		586 (49.8)	236 (44.6)	58 (46.5)	201 (56.5)	91 (55.0)

Associations of physical activity and body mass index with glycated haemoglobin

Any Prescribed Medication ‡					
No	503 (47.7)	278 (58.0)	57 (49.3)	129 (40.1)	39 (28.5)
Yes	606 (52.3)	215 (42.0)	61 (50.7)	214 (59.9)	116 (71.5)
Accelerometer Wear-Time † (no. of minutes/valid day)	867.7 (72.1)	873.2 (68.9)	870.4 (77.1)	854.9 (74.7)	875.1 (69.3)
Total Accumulated Moderate-to-Vigorous-Intensity Physical Activity Time † (no. of minutes/valid day)	30.8 (25.8)	47.2 (25.5)	41.3 (18.6)	11.5 (6.4)	9.7 (5.9)
Moderate-to-Vigorous-Intensity Physical Activity Time in Bouts of ≥10 Minutes † (no. of minutes/valid day)	10.8 (16.2)	39.8 (22.0)	36.4 (11.7)	5.6 (6.1)	4.5 (5.8)
Number of Valid Days ‡					
4	46 (4.5)	17 (3.9)	9 (8.0)	12 (3.5)	8 (6.1)
5	80 (7.5)	32 (6.7)	5 (4.3)	31 (9.3)	12 (8.5)
6	209 (19.7)	89 (18.4)	20 (18.0)	77 (24.1)	23 (15.8)
7	774 (68.3)	355 (71.0)	84 (69.7)	223 (63.1)	112 (69.6)
Glycated Haemoglobin (HbA1c)					
[mmol/mol] †	38.1 (7.3)	36.1 (4.9)	38.5 (4.8)	39.2 (9.2)	41.9 (8.7)
[%] †	5.63 (0.67)	5.45 (0.45)	5.67 (0.44)	5.74 (0.84)	5.98 (0.79)

All analyses controlled for primary sampling units, clustering and survey weights.

† *Continuous variable; Mean (Standard Deviation)*

‡ *Categorical variable; n (Proportion (%))*

Continuous measures of MVPA and BMI

Table 2 displays the associations between continuous measures of total accumulated MVPA time, BMI and HbA1c. In the maximally adjusted model, every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.07% ($p<0.001$)] lower HbA1c level. Each 1 kg/m^2 increment in BMI was associated with a

0.2 mmol/mol [0.02% (p<0.001)] higher HbA1c level. Results were not modified by age (p=0.104 for age x MVPA interaction; p=0.300 for age x BMI interaction) or sex (p=0.975 for sex x MVPA interaction; p=0.170 for sex x BMI interaction). However, the MVPA x BMI interaction term was significant (p=0.004). Table 3 displays the associations of MVPA with HbA1c stratified by BMI status, and the associations of BMI with HbA1c stratified by MVPA status. The association of MVPA with HbA1c was stronger in obese individuals, where every 30 minutes/day increment in MVPA was associated with a 1.5 mmol/mol [0.13% (p<0.001)] lower HbA1c level. In non-obese individuals, every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.06% (p<0.001)] lower HbA1c level. In contrast, the association of BMI with HbA1c remained stable across MVPA categories.

Associations of physical activity and body mass index with glycated haemoglobin

Table 2 - Adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and body mass index (BMI) with glycated haemoglobin (HbA1c)

Adjusted linear regression model	HbA1c (dual units)	MVPA (30 minutes/day)		BMI (1 kg/m^2)	
		Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
Model 1	[mmol/mol] [%]	**-0.9 (-1.4, -0.4)** **-0.08 (-0.13, -0.04)**	**<0.001**	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**
Model 2	[mmol/mol] [%]	**-0.7 (-1.2, -0.2)** **-0.07 (-0.11, -0.02)**	**<0.001**	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**

*All analyses controlled for primary sampling units, clustering and survey weights. **Bold** indicates statistical significance at p<0.01. Model 1 adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time. Model 2 additionally adjusted for BMI (for MVPA analysis) and MVPA (for BMI analysis).*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m^2 increment in BMI*

Associations of physical activity and body mass index with glycated haemoglobin

Table 3 - Interaction analysis: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and body mass index (BMI) with glycated haemoglobin (HbA1c) stratified by MVPA and BMI levels

P-value of MVPA x BMI interaction term	Stratification	HbA1c (dual units)	MVPA (30 minutes/day) Beta (99% CI) †	MVPA (30 minutes/day) p-value	BMI (1 kg/m^2) Beta (99% CI) ‡	BMI (1 kg/m^2) p-value
0.004	BMI <30.0 kg/m^2	[mmol/mol] [%]	**-0.7 (-1.2, -0.1)** **-0.06 (-0.11, -0.01)**	**0.002**	-	-
	BMI ≥30.0 kg/m^2	[mmol/mol] [%]	**-1.5 (-2.3, -0.6)** **-0.13 (-0.21, -0.05)**	**<0.001**	-	-
	MVPA <150 mins/week	[mmol/mol] [%]	-	-	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**
	MVPA ≥150 mins/week	[mmol/mol] [%]	-	-	**0.2 (0.1, 0.3)** **0.02 (0.01, 0.03)**	**<0.001**

All analyses controlled for primary sampling units, clustering and survey weights. ***Bold*** *indicates statistical significance at p<0.01. Models adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

Associations of physical activity and body mass index with glycated haemoglobin

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m^2 increment in BMI*

Mutually exclusive categories of MVPA and BMI

Table 4 shows the differences in HbA1c levels between mutually exclusive categories of total accumulated MVPA time and BMI. Compared with individuals who were 'physically inactive & obese', those who were 'physically active & obese' or 'physically active & non-obese' had significantly lower HbA1c levels by 2.1 mmol/mol [0.19% (p=0.005)] and 3.5 mmol/mol [0.32% (p<0.001)], respectively. However, average HbA1c levels were not significantly different between the 'physically inactive & non-obese' and 'physically inactive and obese' categories.

Associations of physical activity and body mass index with glycated haemoglobin

Table 4 - Adjusted linear regression model showing the associations between mutually exclusive categories of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and body mass index (BMI) with glycated haemoglobin (HbA1c)

HbA1c (dual units)	'Physically active & non-obese'		'Physically active & obese'		'Physically inactive & non-obese'		'Physically inactive & obese'
	Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	
[mmol/mol] [%]	**-3.5 (-5.2, -1.9)** **-0.32 (-0.47, -0.18)**	**<0.001**	**-2.1 (-4.1, -0.2)** **-0.19 (-0.37, -0.02)**	**0.005**	-1.9 (-3.8, 0.0) -0.17 (-0.35, 0.00)	0.012	Reference

All analyses controlled for primary sampling units, clustering and survey weights.

'Physically active' was defined as: ≥150 minutes/week of total accumulated MVPA.

'Physically inactive' was defined as: <150 minutes/week of total accumulated MVPA.

'Obese' was defined as: BMI ≥30.0 kg/m^2.

'Non-obese' was defined as: BMI <30.0 kg/m^2.

***Bold** indicates statistical significance at p<0.01. Model adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) in comparison to the 'physically inactive and obese' category*

Sensitivity analysis

Sensitivity analyses indicated robustness. When waist circumference was used in place of BMI, the pattern of results was unchanged (see online supplementary materials - Table S3). The results were not modified by age (p=0.069 for age x MVPA interaction; p=0.922 for age x waist circumference interaction) or sex (p=0.923 for sex x MVPA interaction; p=0.483 for sex x waist circumference interaction). However, the pattern of results was exaggerated for the MVPA x waist circumference interaction analysis (p<0.001 for interaction; see online supplementary materials - Table S4). In those with high waist circumference, every 30 minutes/day increment in MVPA was associated with a 1.8 mmol/mol [0.16% (p<0.001)] lower HbA1c level. The other sensitivity analyses also indicated stability; although the prevalence in each category varied across the different methods used (see online supplementary materials - Table S5), the key findings were largely unaffected (see online supplementary materials - Table S6).

DISCUSSION

This study quantified the independent and combined associations of objectively measured MVPA and BMI with HbA1c in a sample of English adults. Both MVPA and BMI were independently associated with HbA1c; every 30 minutes/day increment in MVPA was associated with a 0.7 mmol/mol [0.07%] lower HbA1c level and each 1 kg/m^2 increment in BMI was associated with a 0.2 mmol/mol [0.02%] higher HbA1c level. Results for MVPA were modified by BMI status, with a stronger association seen in obese individuals. For those with a BMI of 30.0 kg/m^2 or higher, every 30 minutes/day increment in MVPA was associated with a 1.5 mmol/mol [0.13%] lower

HbA1c level. Compared to individuals categorised as 'physically inactive & obese', only those categorised as 'physically active & obese' or 'physically active & non-obese' had lower HbA1c levels by 2.1 mmol/mol [0.19%] and 3.5 mmol/mol [0.32%], respectively.

Strengths and limitations

Our study has several strengths, which include: the use of HbA1c, a validated and clinically employed measure of glycaemic status; a well-characterised national survey which employs a multifaceted stratified random sampling procedure; examining age and sex interactions; and a range of sensitivity analyses. The key limitation resides in the cross-sectional design which eliminates the possibility of establishing causality. In addition, although we adjusted for a wide range of important lifestyle, demographic and clinical variables, it is possible that unmeasured factors were confounding the reported associations. Generalizability could also be limited by the amount of missing biochemical and covariate data, as well as the small fraction of participants who were asked to wear an accelerometer. However, the key demographics (age, BMI, sex) of the included sample in this study were similar to the full 2008 HSE adult cohort.[20] Even though HbA1c is an established clinical measure of glycaemia that reflects average glucose concentrations over the previous 2-3 months, it is not a perfect index of blood glucose for all individuals, and it does not adequately reflect the glycaemic control status in some diseases that change the life span of erythrocytes, such as chronic liver disease.[21] In addition, although the inclusion of objectively measured MVPA is a notable strength, the device used also has some limitations. Reliance on vertical accelerations to quantify movement and lack of waterproofing means that some activities like cycling may not have been

adequately captured whereas others like swimming were not captured at all. However, ambulation, which makes up the vast majority of human movement, is accurately assessed by accelerometers. Furthermore, cycling and swimming can be considered to be atypical activities in this cohort; with only a small proportion of participants reporting any cycling or swimming activities at all.[12]

Other studies

Our findings extend previous research using HSE data which have reported an association between MVPA and HbA1c in a subsample of older adults.[22] The study also found that neither self-reported or accelerometer assessed sedentary time was associated with HbA1c. Others have also reported a lack of association between sedentary time and HbA1c in HSE using both objective and self-reported data.[23] However, previous studies using HSE did not examine the independent association or modifying effect of BMI. This contrasts with the strong and consistent association reported in the present study for MVPA, suggesting that MVPA may be the stronger determinant of HbA1c in HSE. Our findings are also are consistent with analyses of NHANES which have shown that there was no statistical difference in HbA1c between active obese adults and inactive normal weight adults, with a further analysis showing that an association between MVPA and HbA1c was only present in those with a moderate or high risk of type 2 diabetes;[24 25] however, neither of these studies formally tested for an interaction with BMI. By showing the association of MVPA with HbA1c is stronger in obese adults, our results suggest that MVPA may have greater potential to moderate glycaemic status at higher levels of BMI and confirms previous research suggesting that active obese adults have healthier levels of HbA1c than inactive obese adults. The difference in HbA1c across the mutually

exclusive categories and for every 30 minutes/day increment in MVPA observed for obese individuals in our study is likely to be clinically meaningful beyond diabetes risk. For example, in adults without diabetes, each 0.1% unit increment in HbA1c has been associated with a 2% higher risk of mortality and a 4% higher risk of coronary heart disease or stroke.[26]

Interpretations

Our finding that MVPA may be metabolically protective in obese individuals is also consistent with studies that have shown that cardiorespiratory fitness, which is partly moderated by MVPA, is also an important determinant of metabolic health in obesity.[11] Other studies have consistently reported that obese individuals with moderate to high fitness have a lower risk of all-cause and cardiovascular mortality those with normal BMI but low fitness.[27] However, the extent to which MVPA and fitness can reduce the excess risks of obesity remains controversial,[28] supporting the need for further research in this area. Our results are supported by intervention studies and known mechanistic pathways linking reduced adiposity and higher physical activity to better glucose control and reduced insulin resistance.[3 29-32] The impact of physical activity on glucose levels and insulin resistance in obesity may also be enhanced by preferentially shifting the storage of excess fat away from metabolically active sites, such as within visceral compartments or organs, without effecting overall level adiposity.[33]

Whilst intervention studies have established and quantified the effects on HbA1c levels following interventions aimed at increasing physical activity or reducing body weight in individuals with T2DM,[7-9] the associations between these factors in the

general population are less clear. This is an important limitation as diabetes prevention recommendations and programmes within routine care are increasingly moving towards identifying and referring individuals on the basis of HbA1c whilst also evaluating effectiveness through changes to HbA1c.[4-6] The latter point is particularly important as there is a lack of data supporting the magnitude of potential differences in HbA1c anticipated with specific differences in health behaviours.

Conclusions

In conclusion, this study quantifies the association between MVPA, BMI and HbA1c and shows that the association of MVPA with HbA1c is stronger in those with higher BMI levels. Finding ways of translating this information into encouraging obese people to increase their physical activity levels as an intervention for lowering HbA1c might be important to improve public health and allow for more personalised educational and lifestyle interventions to be implemented. However, given the limitations which preclude inferences of causality, these conclusions need to be confirmed by interrogating data from completed diabetes prevention trials or through further experimental studies.

DECLARATIONS

Ethics approval and consent to participate

Ethical approval for the 2008 Health Survey for England study was obtained from the Oxford A Research Ethics Committee (reference number: 07/H0604/102). Participants provided written informed consent.

Data sharing statement

Permission to use the 2008 Health Survey for England accelerometer data files can be obtained from the National Centre for Social Research (NatCen) (http://www.natcen.ac.uk/). All other data are openly available to download from the UK Data Archive (https://discover.ukdataservice.ac.uk/series/?sn=2000021).

Competing interests

SJHB: Funding has been received since 2012 for consultancy work from Fitness First, Nuffield Health, Unilever, and Weight Watchers, and for travel from The Coca Cola Foundation. None of these are currently active. Funding was received in 2016 for consultancy work for Halpern Limited. A sit-to-stand desk was kindly provided by Ergotron from 2012-2014. Advice has been requested by and offered to Active Working and Get Britain Standing. TY, MJD and KK: Developed a prevention programme, Let's Prevent Diabetes, selected to be part of Healthier You: The NHS Diabetes Prevention Programme in collaboration with Ingeus UK Limited. KK also chaired NICE guidance for the prevention of type 2 diabetes mellitus (PH 38), with TY and MJD part of the committee. All other authors declare that they have no competing interests.

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Authors' contributions

TY had the original idea for the analysis, which was further developed and refined by KB, CLE, DHB, DWE, JMRG, AK, LV, AJS, NS, SJHB, MH, MJD and KK. CLE processed the 2008 Health Survey for England accelerometer data. KB carried out the statistical analysis and worked with TY to write the first and revised drafts of the manuscript. KB, TY, CLE, DHB, DWE, JMRG, AK, LV, AJS, NS, SJHB, MH, MJD and KK edited and reviewed the manuscript drafts. KB, TY, CLE, DHB, DWE, JMRG, AK, LV, AJS, NS, SJHB, MH, MJD and KK approved the final version of the manuscript.

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Research Unit (NIHR DLPA BRU) based at University Hospitals of Leicester and Loughborough University, the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care – East Midlands (NIHR CLAHRC – EM) and the Leicester Clinical Trials Unit (LCTU). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health (DoH).

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SUPPLEMENTARY MATERIALS

Associations of moderate-to-vigorous-intensity physical activity and body mass index with glycated haemoglobin within the general population: a cross-sectional analysis of the 2008 Health Survey for England

Authors: Kishan Bakrania*, Thomas Yates*, Charlotte L. Edwardson, Danielle H. Bodicoat, Dale W. Esliger, Jason M.R. Gill, Aadil Kazi [2, 3], Latha Velayudhan, Alan J. Sinclair, Naveed Sattar, Stuart J.H. Biddle, Mark Hamer, Melanie J. Davies and Kamlesh Khunti

* = joint first authors

Corresponding author: Dr. Charlotte L. Edwardson, Diabetes Research Centre, University of Leicester, Leicester General Hospital, Gwendolen Road, Leicester, Leicestershire, LE5 4PW, United Kingdom. Phone: +44(0)116 258 8577. Email: ce95@le.ac.uk.

Number of supplementary figures: 1

Figure S1 - Flow chart of study participants

Number of supplementary tables: 6

Table S1 - Confounder analysis based on the criteria of changing the regression coefficient for either total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time or body mass index (BMI) by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time

Table S2 - Sample of adults with valid accelerometer data: comparison of the basic characteristics between the included and excluded participants

Table S3 - Sensitivity analyses: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c)

Table S4 - Sensitivity analyses: interaction analysis: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c) stratified by MVPA and waist circumference levels

Table S5 - Sensitivity analyses: weighted mutually exclusive category prevalence

Table S6 - Sensitivity analyses: adjusted linear regression models showing the associations between mutually exclusive categories of moderate-to-vigorous-intensity physical activity (MVPA) time and obesity status with glycated haemoglobin (HbA1c)

Figure S1 - Flow chart of study participants

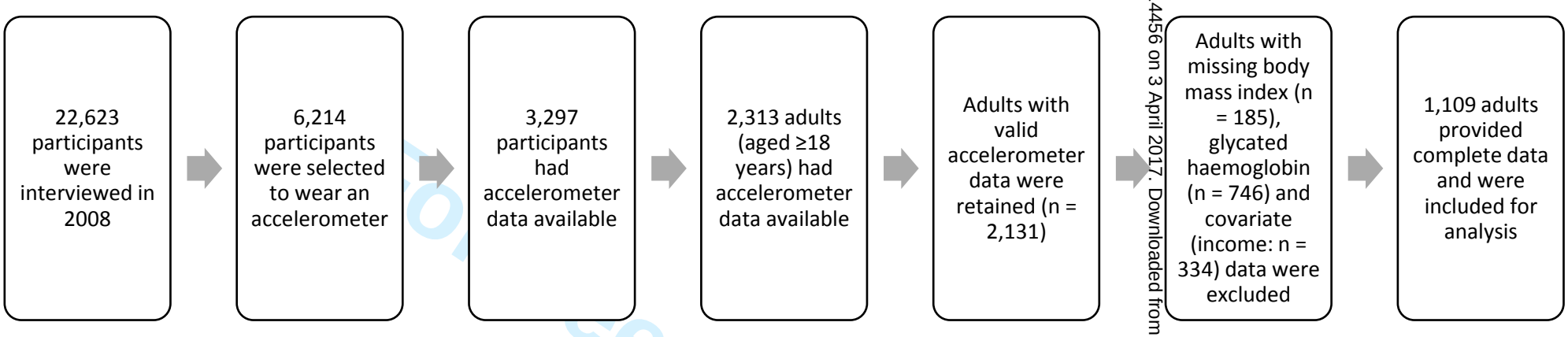

Table S1 - Confounder analysis based on a criteria of changing the regression coefficient for either total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time or body mass index (BMI) by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex and accelerometer wear-time

		MVPA (30 minutes/day): Beta †	% Change in MVPA Beta	BMI (1 kg/m^2): Beta ‡	% Change in BMI Beta
HbA1c (dual units)	[mmol/mol]	-1.08619	-	0.27118	-
	[%]	-0.09939		0.02481	
Covariate individually added to basic model (age, sex, ethnicity and accelerometer wear-time)					
Disease index		-1.00775	7.2	0.26435	-2.5
		-0.09221		0.02419	
Reported fruit & vegetable consumption		-1.09698	-1.0	0.26803	-1.2
		-0.10037		0.02452	
Income		-1.06915	1.6	**0.23041**	**-15.0**
		-0.09783		**0.02108**	
Smoking status		-1.05337	3.0	0.28741	6.0
		-0.09638		0.02630	
Socioeconomic status		-1.15279	-6.1	0.26994	-0.5
		-0.10548		0.02470	
Any prescribed medication		**-0.97137**	**10.6**	0.25601	-5.6
		-0.08888		0.02343	

Sedentary time	-1.18817 -0.10872	-9.4	0.27613 0.02472	-0.4
Light-intensity physical activity time	-1.11946 -0.10243	-3.1	0.27152 0.02484	0.1

All analyses controlled for primary sampling units, clustering and survey weights. Confounders were considered for inclusion as follows: primarily using all the available data, in separate models for MVPA and BMI with glycated haemoglobin (HbA1c) as the dependent variable, confounders were included based on a criteria of changing the regression coefficient for either MVPA or BMI by 10% or more once added individually to a basic model adjusted for age, ethnicity, sex, and accelerometer wear-time. ***Bold*** *indicates a ≥10% change in the regression coefficient for either MVPA or BMI.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m^2 increment in BMI*

Table S2 - Sample of adults with valid accelerometer data: comparison of the basic characteristics between the included and excluded participants

Characteristic	Included (N = 1,109)	Excluded (N = 1,022)	p-value
Age (in years) †	51.0 (16.5)	50.6 (18.8)	0.601
Body Mass Index (kg/m^2) †	27.3 (4.8)	27.7 (5.4)	0.085
Missing	0 (0.0)	185 (18.1)	
Waist Circumference (cm) †	92.9 (13.9)	94.0 (15.0)	0.100
Missing	0 (0.0)	229 (22.4)	
Ethnicity ‡			0.063
White	1,055 (94.2)	953 (92.1)	
Non-White	54 (5.8)	69 (7.9)	
Sex ‡			0.278
Men	523 (50.2)	458 (48.3)	
Women	586 (49.8)	564 (51.7)	
Total Accumulated Moderate-to-Vigorous-Intensity Physical Activity Time † (no. of minutes/valid day)	30.8 (25.8)	29.7 (24.9)	0.318
Moderate-to-Vigorous-Intensity Physical Activity Time in Bouts of ≥10 Minutes † (no. of minutes/valid day)	10.8 (16.2)	10.0 (14.6)	0.233

All analyses controlled for primary sampling units, clustering and survey weights.

† *Continuous variable; Mean (Standard Deviation); p-value based on unpaired t-test*

‡ *Categorical variable; n (Proportion (%)); p-value based on chi-squared test*

Bold *indicates statistical significance at p<0.05*

Table S3 - Sensitivity analyses: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c)

Adjusted linear regression model	HbA1c (dual units)	MVPA (30 minutes/day)		Waist Circumference (1 cm)	
		Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
Model 1	[mmol/mol] [%]	**-0.9 (-1.4, -0.4)** **-0.08 (-0.13, -0.03)**	**<0.001**	**0.1 (0.1, 0.1)** **0.01 (0.01, 0.01)**	**<0.001**
Model 2	[mmol/mol] [%]	**-0.6 (-1.0, -0.1)** **-0.05 (-0.10, -0.01)**	**0.003**	**0.1 (0.1, 0.1)** **0.01 (0.01, 0.01)**	**<0.001**

*All analyses controlled for primary sampling units, clustering and survey weights. **Bold** indicates statistical significance at p<0.01. Model 1 adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time. Model 2 additionally adjusted for waist circumference (for MVPA analysis) and MVPA (for waist circumference analysis).*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 cm increment in waist circumference*

Table S4 - Sensitivity analyses: interaction analysis: adjusted linear regression models showing the associations between continuous measures of total accumulated moderate-to-vigorous-intensity physical activity (MVPA) time and waist circumference with glycated haemoglobin (HbA1c) stratified by MVPA and waist circumference levels

P-value of MVPA x Waist Circumference interaction term	Stratification	HbA1c (dual units)	MVPA (30 minutes/day)		Waist Circumference (1 cm)	
			Beta (99% CI) †	p-value	Beta (99% CI) ‡	p-value
<0.001	Low Waist Circumference	[mmol/mol] [%]	-0.3 (-0.7, 0.0) -0.03 (-0.06, 0.00)	0.024	-	-
	High Waist Circumference	[mmol/mol] [%]	**-1.8 (-3.0, -0.5)** **-0.16 (-0.28, -0.05)**	**<0.001**	-	-
	MVPA <150 mins/week	[mmol/mol] [%]	-	-	**0.1 (0.1, 0.2)** **0.01 (0.01, 0.02)**	**<0.001**
	MVPA ≥150 mins/week	[mmol/mol] [%]	-	-	**0.1 (0.0, 1)** **0.01 (0.00, 0.01)**	**<0.001**

All analyses controlled for primary sampling units, clustering and survey weights. 'High Waist Circumference' was defined as having a waist circumference of ≥102 cm for men and ≥88 cm for women. ***Bold*** *indicates statistical significance at p<0.01. Models adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 30 minutes/day increment in MVPA*

‡ *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 cm increment in waist circumference*

Table S5 - Sensitivity analyses: weighted mutually exclusive category prevalence

	Weighted Prevalence [%]			
Method	'Physically active & non-obese'	'Physically active & obese'	'Physically inactive & non-obese'	'Physically inactive & obese'
Reference	45.9%	10.7%	29.9%	13.5%
1	37.8%	19.0%	20.0%	23.2%
2	36.1%	20.5%	20.7%	22.7%
3	14.3%	1.8%	61.5%	22.4%

All analyses controlled for primary sampling units, clustering and survey weights.

Reference Method = Mutually exclusive categories derived and utilised in the main analysis

Method 1 = 'Obese' was defined as having a waist circumference of ≥102 cm for men and ≥88 cm for women

Method 2 = 'Obese' was defined as having a body mass index of ≥27.5 kg/m²

Method 3 = Participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes

Table S6 - Sensitivity analyses: adjusted linear regression models showing the associations between mutually exclusive categories of moderate-to-vigorous-intensity physical activity (MVPA) time and obesity status with glycated haemoglobin (HbA1c)

Method	HbA1c (dual units)	'Physically active & non-obese'		'Physically active & obese'		'Physically inactive & non-obese'		'Physically inactive & obese'
		Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	Beta (99% CI) †	p-value	
Reference	[mmol/mol] [%]	**-3.5 (-5.2, -1.9)** **-0.32 (-0.47, -0.18)**	**<0.001**	**-2.1 (-4.1, -0.2)** **-0.19 (-0.37, -0.02)**	**0.005**	-1.9 (-3.8, 0.0) -0.17 (-0.35, 0.00)	0.012	Reference
1	[mmol/mol] [%]	**-4.1 (-5.9, -2.2)** **-0.37 (-0.54, -0.21)**	**<0.001**	**-2.5 (-4.4, -0.6)** **-0.23 (-0.40, -0.05)**	**0.001**	**-3.1 (-5.0, -1.2)** **-0.29 (-0.46, -0.11)**	**<0.001**	Reference
2	[mmol/mol] [%]	**-2.9 (-4.1, -1.7)** **-0.27 (-0.38, -0.16)**	**<0.001**	**-1.5 (-2.9, -0.2)** **-0.14 (-0.27, -0.02)**	**0.004**	-0.9 (-2.9, 1.1) -0.08 (-0.27, 0.01)	0.229	Reference
3	[mmol/mol] [%]	**-3.4 (-4.7, -2.1)** **-0.31 (-0.43, -0.20)**	**<0.001**	-2.0 (-4.3, 0.3) -0.18 (-0.39, 0.03)	0.027	**-1.7 (-3.0, -0.4)** **-0.16 (-0.28, -0.04)**	**0.001**	Reference

All analyses controlled for primary sampling units, clustering and survey weights.

Reference Method = Mutually exclusive categories derived and utilised in the main analysis

Method 1 = 'Obese' was defined as having a waist circumference of ≥102 cm for men and ≥88 cm for women

Method 2 = 'Obese' was defined as having a body mass index of ≥27.5 kg/m²

Method 3 = Participants were only classified into the 'physically active' categories if they accumulated ≥150 minutes/week of MVPA in bouts of ≥10 minutes

***Bold** indicates statistical significance at p<0.01. Models adjusted for: age, ethnicity, income, sex, any prescribed medication, and accelerometer wear-time.*

† *Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) in comparison to the 'physically inactive and obese' category*

STROBE Statement - Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page(s): 1 Line number(s): 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page(s): 4-5 Line number(s): 75-106
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page(s): 7-8 Line number(s): 149-179
Objectives	3	State specific objectives, including any prespecified hypotheses	Page(s): 7-8 Line number(s): 171-179
Methods			
Study design	4	Present key elements of study design early in the paper	Page(s): 8-11 Line number(s): 182-250
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page(s): 8-11 Line number(s): 182-250
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page(s): 8-12 Line number(s): 182-283
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page(s): 8-14 Line number(s): 182-329
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page(s): 8-14 Line number(s): 182-329
Bias	9	Describe any efforts to address potential sources of bias	Page(s): 8, 11 Line number(s): 185-187 Line number(s): 253-256
Study size	10	Explain how the study size was arrived at	Page(s): 8, 11-12 Line number(s): 190-192 Line number(s): 271-277

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page(s): 11-14 Line number(s): 258-329
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page(s): 11-14 Line number(s): 252-329
		(*b*) Describe any methods used to examine subgroups and interactions	Page(s): 12-14 Line number(s): 297-329
		(*c*) Explain how missing data were addressed	Page(s): 11-12 Line number(s): 258-277
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Page(s): 11 Line number(s): 253-256
		(*e*) Describe any sensitivity analyses	Page(s): 13-14 Line number(s): 320-329
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page(s): 8, 11-12 Line number(s): 190-192 Line number(s): 271-277
		(b) Give reasons for non-participation at each stage	Page(s): 8, 11-12 Line number(s): 190-192 Line number(s): 271-277
		(c) Consider use of a flow diagram	Page(s): 8, 12 Line number(s): 190-192 Line number(s): 273-276
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Page(s): 14-16 Line number(s): 332-347
		(b) Indicate number of participants with missing data for each variable of interest	Page(s): 11-12 Line number(s): 271-273
Outcome data	15*	Report numbers of outcome events or summary measures	Page(s): 14-16 Line number(s): 332-347
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page(s): 16-18 Line number(s): 349-369

		(*b*) Report category boundaries when continuous variables were categorized	Page(s): 12-14 Line number(s): 297-329
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done - e.g. analyses of subgroups and interactions, and sensitivity analyses	Page(s): 19-23 Line number(s): 371-402
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page(s): 23-24 Line number(s): 405-417
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page(s): 24-25 Line number(s): 423-443
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page(s): 25-27 Line number(s): 445-494
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page(s): 24-27 Line number(s): 405-505
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page(s): 29 Line number(s): 539-542

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.