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BMJ Open 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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ABSTRACT

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 1109 participants aged ≥ 18 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 and non-obese', (2) 'physically active and obese', (3) 'physically inactive and non-obese' and (4) 'physically inactive and obese'. 'Physically active' was defined as: ≥ 150 min/week of MVPA. 'Obese' was defined as: BMI ≥ 30.0 kg/m². A wide range of sensitivity analyses were also implemented.

Results: Every 30 min/day increment in MVPA was associated with a 0.7 mmol/mol (0.07% ($p < 0.001$)) lower HbA1c level. Each 1 kg/m² 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 with individuals categorised as 'physically inactive and obese', only those categorised as 'physically active and obese' or 'physically active and non-obese' had lower HbA1c levels by 2.1 mmol/mol (0.19% ($p = 0.005$)) and

Strengths and limitations of this study

- This study uses 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.

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.

INTRODUCTION

Diabetes mellitus is one of the most prevalent and costly chronic conditions accounting for between 7% and 14% of healthcare funding globally.¹ This healthcare 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 healthcare 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, while 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 hypothesise that MVPA may provide a metabolically protective effect in obese individuals; since cardio-respiratory 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} 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 2313 adults (aged ≥ 18) were available, with 2131 adults providing valid accelerometer data (see online supplementary materials figure S1). Participants provided written informed consent. 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 1 min 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/min), light-intensity physical activity (≥ 100 to < 1952 counts/min) and sedentary behaviour (< 100 counts/min).^{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.

While time in total accumulated MVPA was used for the primary analysis, MVPA time accumulated in bouts of ≥ 10 min (allowing for a 2 min exception in the intensity threshold) was also derived for a sensitivity analysis (see *Statistical analysis—Sensitivity analysis*).

Body mass index (BMI)

A trained fieldworker recorded height (measured to the nearest 0.1 cm) and weight (measured to the nearest 0.1 kg 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*).

Glycated haemoglobin (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 used: 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) 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, 1109 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=1109) were tabulated. Categorical variables were presented as numbers and proportions, whereas continuous variables were summarised as means and SDs. 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 min) 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 min/day increments) or BMI (presented as of

1 kg/m² 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 min/week of MVPA; and at a BMI threshold of 30.0 kg/m²).

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 min/week of MVPA, respectively. BMI status was determined as 'non-obese' or 'obese' on the basis of a BMI threshold of 30.0 kg/m² (ie, non-obese if BMI < 30.0 kg/m² and obese if BMI ≥ 30.0 kg/m²). These categories allowed four mutually exclusive groups: (1) 'physically active and non-obese', (2) 'physically active and obese', (3) 'physically inactive and non-obese' and (4) 'physically inactive and 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 (ie, age, ethnicity, income, sex, any prescribed medication and accelerometer wear-time).

All reported p values were two sided, and 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% CIs) in HbA1c.

Sensitivity analysis

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/m² for the mutually exclusive categorical data; and (3) Participants were only classified into the 'physically active' categories if they accumulated ≥ 150 min/week of MVPA in bouts of ≥ 10 min for the mutually exclusive categorical data.

RESULTS

Participant characteristics

Table 1 displays the characteristics of the included 1109 participants (mean age (SD)=51.0 (16.5) years; mean BMI (SD)=27.3 (4.8) kg/m²; mean total accumulated MVPA time (SD)=30.8 (25.8) minutes) across the derived mutually exclusive categories of MVPA and BMI.

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 min/day increment in MVPA was associated with a 0.7 mmol/mol (0.07% (p<0.001)) lower HbA1c level. Each 1 kg/m²

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 × MVPA interaction; p=0.300 for age × BMI interaction) or sex (p=0.975 for sex × MVPA interaction; p=0.170 for sex × BMI interaction). However, the MVPA × 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 min/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 min/day increment in MVPA was associated with

Table 1 Participant characteristics

Characteristic	Sample N=1109	'Physically active and non-obese' n=493; 45.9%	'Physically active and obese' n=118; 10.7%	'Physically inactive and non-obese' n=343; 29.9%	'Physically inactive and obese' 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	1055 (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* (number 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* (number 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 min* (number 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 (SD).

†Categorical variable; n (proportion (%)).

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 min/day)		BMI (1 kg/m ²)	
		Beta (99% CI)*	p Value	Beta (99% CI)†	p Value
Model 1	(mmol/mol)	-0.9 (-1.4 to -0.4)	<0.001	0.2 (0.1 to 0.3)	<0.001
	(%)	-0.08 (-0.13 to -0.04)		0.02 (0.01 to 0.03)	
Model 2	(mmol/mol)	-0.7 (-1.2 to -0.2)	<0.001	0.2 (0.1 to 0.3)	<0.001
	(%)	-0.07 (-0.11 to -0.02)		0.02 (0.01 to 0.03)	

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 min/day increment in MVPA.

†Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m² increment in BMI.

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 × BMI interaction term	Stratification	HbA1c (dual units)	MVPA (30 min/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 to -0.1)	0.002	–	–
		(%)	-0.06 (-0.11 to -0.01)			
	BMI ≥ 30.0 kg/m ²	(mmol/mol)	-1.5 (-2.3 to -0.6)	<0.001	–	–
		(%)	-0.13 (-0.21 to -0.05)			
	MVPA < 150 mins/week	(mmol/mol)	–	–	0.2 (0.1 to 0.3)	<0.001
		(%)			0.02 (0.01 to 0.03)	
	MVPA ≥ 150 mins/week	(mmol/mol)	–	–	0.2 (0.1 to 0.3)	<0.001
		(%)			0.02 (0.01 to 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 min/day increment in MVPA.

†Beta coefficients represent the average difference in HbA1c (mmol/mol) (%) for each 1 kg/m² increment in BMI.

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.

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 and obese', those who were 'physically active and obese' or 'physically active and 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 and non-obese' and 'physically inactive and obese' categories.

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 × MVPA interaction; $p = 0.922$ for age × waist circumference interaction) or sex ($p = 0.923$ for sex × MVPA interaction; $p = 0.483$ for sex × waist

circumference interaction). However, the pattern of results was exaggerated for the MVPA × waist circumference interaction analysis ($p < 0.001$ for interaction; see online supplementary materials table S4). In those with high waist circumference, every 30 min/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. MVPA and BMI were independently associated with HbA1c; every 30 min/day increment in MVPA was associated with a 0.7 mmol/mol (0.07%) lower HbA1c level and each 1 kg/m² 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

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 and non-obese'		'Physically active and obese'		'Physically inactive and non-obese'		'Physically inactive and obese'
	Beta (99% CI)*	p Value	Beta (99% CI) *	p Value	Beta (99% CI)*	p Value	
(mmol/mol)	-3.5 (-5.2 to -1.9)	<0.001	-2.1 (-4.1 to -0.2)	0.005	-1.9 (-3.8 to 0.0)	0.012	Reference
(%)	-0.32 (-0.47 to -0.18)		-0.19 (-0.37 to -0.02)		-0.17 (-0.35 to 0.00)		

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

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

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

'Obese' was defined as: $\text{BMI} \geq 30.0 \text{ kg/m}^2$.

'Non-obese' was defined as: $\text{BMI} < 30.0 \text{ kg/m}^2$.

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.

association seen in obese individuals. For those with a BMI of 30.0 kg/m^2 or higher, every 30 min/day increment in MVPA was associated with a 1.5 mmol/mol (0.13%) lower HbA1c level. Compared with individuals categorised as 'physically inactive and obese', only those categorised as 'physically active and obese' or 'physically active and 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. Generalisability 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 lifespan 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 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 consistent with analyses of National Health and Nutrition Examination Survey (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 min/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

While 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 while 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.

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REFERENCES

- Zhang P, Zhang X, Brown J, *et al*. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:293–301.
- Hex N, Bartlett C, Wright D, *et al*. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med* 2012;29:855–62.
- Gillies CL, Abrams KR, Lambert PC, *et al*. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. *BMJ* 2007;334:299.
- National Health Service England. NHS Diabetes Prevention Programme (NHS DPP). 2015. <https://http://www.england.nhs.uk/ourwork/qual-clin-lead/diabetes-prevention/> (accessed 30 Jan 2017).
- World Health Organisation. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Abbreviated report of a WHO consultation. 2011. http://www.who.int/diabetes/publications/report-hba1c_2011.pdf?ua=1 (accessed 30 Jan 2017).
- National Institute for Health and Care Excellence. Type 2 diabetes: prevention in people at high risk. 2012. <https://www.nice.org.uk/guidance/ph38> (accessed 30 Jan 2017).
- Wing RR. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: four-year results of the Look AHEAD trial. *Arch Intern Med* 2010;170:1566–75.
- Umpierre D, Ribeiro PA, Kramer CK, *et al*. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2011;305:1790–9.
- Norris SL, Zhang X, Avenell A, *et al*. Pharmacotherapy for weight loss in adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2005;(1):CD004096.
- Gong QH, Kang JF, Ying YY, *et al*. Lifestyle interventions for adults with impaired glucose tolerance: a systematic review and meta-analysis of the effects on glycemic control. *Intern Med* 2015;54:303–10.
- Ortega FB, Lee DC, Katzmarzyk PT, *et al*. The intriguing metabolically healthy but obese phenotype: cardiovascular prognosis and role of fitness. *Eur Heart J* 2013;34:389–97.
- Joint Health Surveys Unit. *Health Survey for England 2008: Volume 1. Physical activity and fitness*. Leeds, UK: The Health and Social Care Information Centre, 2008. <http://content.digital.nhs.uk/catalogue/PUB00430/heal-surv-phys-acti-fitn-eng-2008-rep-v2.pdf> (accessed 30 Jan 2017).
- Joint Health Surveys Unit. *Health Survey for England 2008: Volume 2. Methods and documentation*. Leeds, UK: The Health and Social Care Information Centre, 2008. <http://content.digital.nhs.uk/catalogue/PUB00430/heal-surv-phys-acti-fitn-eng-2008-rep-v3.pdf> (accessed 30 Jan 2017).
- Matthews CE, Chen KY, Freedson PS, *et al*. Amount of time spent in sedentary behaviors in the United States, 2003–2004. *Am J Epidemiol* 2008;167:875–81.
- Freedson PS, Melanson E, Sirard J. Calibration of the computer science and applications, Inc. accelerometer. *Med Sci Sports Exerc* 1998;30:777–81.
- Trost SG, McIver KL, Pate RR. Conducting accelerometer-based activity assessments in field-based research. *Med Sci Sports Exerc* 2005;37(11 Suppl):S531–43.
- Maldonado G, Greenland S. Simulation study of confounder-selection strategies. *Am J Epidemiol* 1993;138:923–36.
- World Health Organisation. Global recommendations on physical activity for health. 2010. http://apps.who.int/iris/bitstream/10665/44399/1/9789241599979_eng.pdf (accessed 30 Jan 2017).
- Department of Health. Start active, stay active. A report on physical activity for health from the four home countries' Chief Medical Officers. 2011. https://http://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216370/dh_128210.pdf (accessed 30 Jan 2017).
- Hamer M, Coombs N, Stamatakis E. Associations between objectively assessed and self-reported sedentary time with mental health in adults: an analysis of data from the Health Survey for England. *BMJ Open* 2014;4:e004580.
- Koga M, Kasayama S, Kanehara H, *et al*. CLD (chronic liver diseases)-HbA1C as a suitable indicator for estimation of mean plasma glucose in patients with chronic liver diseases. *Diabetes Res Clin Pract* 2008;81:258–62.
- Stamatakis E, Davis M, Stathi A, *et al*. Associations between multiple indicators of objectively-measured and self-reported sedentary behaviour and cardiometabolic risk in older adults. *Prev Med* 2012;54:82–7.
- Stamatakis E, Hamer M, Tilling K, *et al*. Sedentary time in relation to cardio-metabolic risk factors: differential associations for self-report vs accelerometry in working age adults. *Int J Epidemiol* 2012;41:1328–37.
- Loprinzi P, Smit E, Lee H, *et al*. The “fit but fat” paradigm addressed using accelerometer-determined physical activity data. *N Am J Med Sci* 2014;6:295–301.
- Gay JL, Buchner DM, Schmidt MD. Dose-response association of physical activity with HbA1c: intensity and bout length. *Prev Med* 2016;86:58–63.
- Selvin E, Steffes MW, Zhu H, *et al*. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 2010;362:800–11.
- Fogelholm M. Physical activity, fitness and fatness: relations to mortality, morbidity and disease risk factors. A systematic review. *Obes Rev* 2010;11:202–21.
- Hogstrom G, Nordstrom A, Nordstrom P. Aerobic fitness in late adolescence and the risk of early death: a prospective cohort study of 1.3 million Swedish men. *Int J Epidemiol* 2016;45:1159–68.
- Norris SL, Zhang X, Avenell A, *et al*. Long-term effectiveness of weight-loss interventions in adults with pre-diabetes: a review. *Am J Prev Med* 2005;28:126–39.
- Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* 2006;444:840–6.
- Hawley JA. Exercise as a therapeutic intervention for the prevention and treatment of insulin resistance. *Diabetes Metab Res Rev* 2004;20:383–93.
- Hamman RF, Wing RR, Edelstein SL, *et al*. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006;29:2102–7.
- Johnson NA, Sachinwalla T, Walton DW, *et al*. Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. *Hepatology* 2009;50:1105–12.