


# Association of accelerometer-measured physical activity and its change with progression to chronic kidney disease in adults with type 2 diabetes and overweight/obesity

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## ABSTRACT

**Objective** To examine the long-term association of objectively measured moderate-to-vigorous physical activity (MVPA) and its longitudinal changes with progression to chronic kidney disease (CKD) in patients with type 2 diabetes (T2D) and overweight/obesity.

**Methods** This study included 1746 participants in the Look AHEAD trial with baseline estimated glomerular filtration rate (eGFR)  $\geq 60$  mL/min/1.73 m<sup>2</sup>. MVPA was measured at baseline, year 1, year 4 and year 8 using an RT3 accelerometer. The outcome was progression to CKD, defined as eGFR  $< 60$  mL/min per 1.73 m<sup>2</sup> with a drop of  $\geq 30\%$  or end-stage kidney disease. Cox hazards models were fitted to examine the association between MVPA and outcomes.

**Results** Over a median follow-up of 12.0 years, 567 participants experienced progression to CKD. Overall, there was a linear inverse association of cumulative average total MVPA (per 100 min/week higher amount, HR: 0.91; 95% CI: 0.86 to 0.96) and MVPA accumulated in bouts of  $\geq 10$  min (per 100 minutes/week higher amount, HR: 0.81; 95% CI: 0.72 to 0.91) with progression to CKD. Moreover, an increase in total MVPA from baseline to year 4 (the fourth quartile,  $\geq 63.2$  min/week) was associated with a 33% lower risk of progression to CKD compared with the largest MVPA reduction (the first quartile,  $< -198.3$  min/week). A lower risk of progression to CKD was also observed for increases in MVPA accumulated in bouts of both  $< 10$  min and  $\geq 10$  min.

**Conclusions** Longer MVPA time and increases in MVPA was associated with a reduced risk of progression to CKD in adults with overweight/obesity and T2D.

## INTRODUCTION

Chronic kidney disease (CKD) is an important public health issue affecting approximately 10% of the world population.<sup>1</sup> Diabetes is the leading cause of CKD, accounting for 30–50% of all CKD cases.<sup>2</sup> Diabetes with CKD is associated with a 10-fold or greater increase in all-cause mortality compared with diabetes alone.<sup>3</sup> Thus, it is paramount to identify cost-effective strategies to prevent the onset of CKD in diabetic.

Physical activity (PA), a modifiable lifestyle behaviour, has been recommended as an important part of diabetes management programmes.<sup>4–5</sup>

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Evidence regarding the association between physical activity (PA) and chronic kidney disease (CKD) risk in participants with type 2 diabetes (T2D) is generally limited due to the use of self-report questionnaires. Moreover, little is known about the renal health benefits of moderate-to-vigorous PA (MVPA) in short episodes lasting  $< 10$  min.

## WHAT THIS STUDY ADDS

⇒ Overall, there was a linear inverse association of cumulative average MVPA, especially MVPA accumulated in bouts of  $\geq 10$  min, with progression to CKD in participants with T2D and overweight/obesity. Moreover, 4-year increase in total MVPA and MVPA accumulated in bouts of  $< 10$  and  $\geq 10$  min were also inversely associated with the risk of progression to CKD.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study suggests that regardless of the length of PA, being physically active is one of the cornerstones to preventing renal disease in T2D, especially for individuals who are unwilling or unable to engage in PA bouts  $\geq 10$  min in duration.

Short-term interventional exercise has been shown to improve renal function in people with diabetes and mild renal dysfunction.<sup>6</sup> However, in terms of long-term benefits, although a few prospective studies have reported that higher PA was associated with improved kidney outcomes in patients with type 2 diabetes (T2D),<sup>7–9</sup> all of these studies have relied on short follow-up periods and one-time self-reported measures of PA, which are prone to recall biases and are relatively imprecise. In contrast, a small-scale study (n=326) showed no association between the 4-year change in objectively measured moderate-to-vigorous PA (MVPA) and kidney function at year 4.<sup>10</sup> Therefore, the long-term association of objectively measured PA, as well as the longitudinal changes in PA, with CKD risk in patients with T2D warrants further investigation.



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Another consideration is whether the pattern of PA accumulation matters. The 2008 Physical Activity Guidelines for Americans recommend accumulating  $\geq 150$  min/week MVPA in bouts lasting  $\geq 10$  min.<sup>11</sup> Recently, the 10 min bout statement have been removed in the USA and WHO guidelines,<sup>12 13</sup> given that most free-living and unstructured MVPA activity is likely performed in episodes typically  $< 10$  min in duration and bouts of PA  $< 10$  min in duration may also have health-related benefits.<sup>14–16</sup> Nevertheless, the majority of studies supporting the health benefits of PA accumulated in bouts of  $< 10$  min in duration have used a cross-sectional design, and little is known about the benefits of short bouts of PA on kidney function.

As a post hoc secondary data analyses from the Look AHEAD trial,<sup>17</sup> the current study aimed to examine the longitudinal association of objectively measured MVPA and changes in MVPA with the risk of progression to CKD in patients with T2D. We also examined whether the association varied when PA was considered in short ( $< 10$  min) and long ( $\geq 10$  min) bouts.

## METHODS

### Study design and participants

The Look AHEAD trial was a multicentre, randomised controlled trial that was conducted at 16 clinical sites in the USA and evaluated the cardiovascular effects of an intensive lifestyle intervention (ILI) in comparison with diabetes support and education (DSE) among 5145 participants with T2D and overweight or obesity (body mass index (BMI)  $\geq 25$  kg/m<sup>2</sup>, or  $\geq 27$  kg/m<sup>2</sup> when taking insulin).<sup>17</sup> Participants were recruited between 2001 and 2004 and randomly assigned to either ILI or DSE, with stratification by clinical site. The intervention was stopped for futility after a median follow-up of 9.6 years. Subsequently, the study was continued as an observational study with additional follow-up extending to July 2020. The design and methods of the Look AHEAD trial have been described in detail previously.<sup>17 18</sup>

The present study is an exploratory post hoc analysis of the Look AHEAD trial and restricted to an accelerometry substudy, which was conducted at 8 of the 16 clinical sites and recruited 51.1% of the total participants in the Look AHEAD.<sup>19</sup> We further excluded participants without valid accelerometry data at baseline, those with baseline estimated glomerular filtration rate (eGFR)  $< 60$  or self-reported kidney failure and those who lacked information for defining progression to CKD during follow-up, resulting in a sample of 1746 participants (online supplemental figure 1).

### Objective assessment of PA

PA was assessed using a triaxial accelerometer (RT3; Stayhealthy, Monrovia, California, USA) at baseline, year 1 and year 4 on the accelerometry substudy.<sup>19</sup> Moreover, objective measures of PA were also collected using the same type of accelerometer and wear protocol at year 8/9 among participants in the Look AHEAD Movement and Memory ancillary study.<sup>20</sup> RT3 has been shown to provide a valid assessment of activity with good intraunit reliability,<sup>21 22</sup> and provide similar estimates of PA compared with other accelerometers.<sup>23 24</sup> In the Look AHEAD trial, the accelerometer was worn vertically at the waist at the anatomical location of the anterior iliac spine for seven consecutive days during waking hours, removing it only for periods of sleep, bathing, showering or other water-based activities. The data collection mode for the accelerometer was set in the three axis and 1 min epoch mode, and various quality control procedures were implemented.<sup>25</sup> Data for a given day were considered

valid if the accelerometer was worn for  $\geq 10$  hours on that day, and at least four valid days of accelerometry data were required in the present analysis.

PA intensity was expressed in metabolic equivalents (METs), calculated by dividing the estimated total energy expenditure per minute by the estimated resting energy expenditure per minute, using proprietary software provided by Stayhealthy that accompanies the RT3 accelerometer.<sup>25</sup> The proprietary algorithm exhibited good classification accuracy for MVPA.<sup>26</sup> Sedentary (SED), light (LPA), moderate (MPA) or vigorous (VPA) PA were defined as any activity of  $< 1.5$  METs,  $\geq 1.5$  and  $< 3$  METs,  $\geq 3$  METs and  $\geq 6$  METs, respectively. Total MVPA was defined as the sum of all minutes that meet the  $\geq 3$  METs criteria, whereas short-bout or long-bout MVPA was defined as the sum of all minutes in bouts of 1–9 min or  $\geq 10$  min that meet the  $\geq 3$  METs criteria, respectively.

## Outcomes

Serum creatinine concentration was accessible annually through year 4 and every other year thereafter during the intervention period, as well as every 2 years during the post-intervention follow-up. Serum creatinine was measured with the Roche Creatinine Plus enzymatic reagent on a Roche Modular P autoanalyzer, and the value of the assay calibrator is traceable to the Isotope Dilution Mass Spectrometry reference method. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation based on serum creatinine that includes race (black vs non-black).<sup>27</sup>

The primary outcome was the progression to CKD, defined as eGFR  $< 60$  mL/min per 1.73 m<sup>2</sup> with at least 30% drop at a follow-up visit relative to baseline, or end-stage renal disease (eGFR  $< 15$  mL/min per 1.73 m<sup>2</sup> or self-reported kidney failure or death from renal failure). Mortality from renal failure was adjudicated according to death certificates, hospitalisation records, informant interviews with relatives and a National Death Index search.

### Additional baseline assessments

Information on age, sex, race, education, employment status, family income, smoking status, alcohol consumption, duration of diabetes and family history of diabetes was ascertained by standardised interviewer-administered questionnaires. Anthropometric measures were obtained by trained and certified clinical staff using standard methods. Weight and height were measured twice separately with a digital scale and a stadiometer, respectively, and the average of these repeated measurements was used for analysis. Blood samples were obtained after at least a 12-hour fast and were analysed by the Central Biochemistry Laboratory using standardised laboratory procedures. The Roche Creatinine Plus enzymatic reagent and Roche Modular P autoanalyzer were used to measure urine creatinine. Urine albumin-to-creatinine ratio (UACR) was calculated from urine albumin and creatinine concentrations.

### Statistical analysis

Population characteristics were presented as mean (SD) for normally distributed continuous variables and medians (IQR) for non-normally distributed continuous variables, and as proportions for categorical variables. Comparison of baseline characteristics according to quartiles of total MVPA was performed using analysis of variance tests, Kruskal-Wallis test, or  $\chi^2$  tests, accordingly.

**Table 1** Population characteristics according to total moderate to vigorous physical activity (MVPA) (N=1746)\*

Characteristics	Total	Quartiles of cumulative average total MVPA, min/week				P value
		Q1 (<220.3)	Q2 (220.3 to <328.8)	Q3 (328.8 to <469.2)	Q4 (≥469.2)	
N	1746	437	436	436	437	
Age, years	58.0 (55.0 to 63.0)	61.0 (56.0 to 66.0)	59.0 (55.0 to 64.0)	57.0 (54.0 to 62.0)	56.0 (52.0 to 61.0)	<0.001
Female, N (%)	1025 (58.7)	318 (72.8)	276 (63.3)	246 (56.4)	185 (42.3)	<0.001
White, N (%)	1294 (74.1)	309 (70.7)	310 (71.1)	341 (78.2)	334 (76.4)	0.090
Intensive lifestyle intervention, N (%)	878 (50.3)	191 (43.7)	224 (51.4)	226 (51.8)	237 (54.2)	0.012
Body mass index, kg/m <sup>2</sup>	35.5 (32 to 39.8)	35.0 (31.6 to 39.1)	35.8 (32.4 to 40.2)	35.5 (31.9 to 40)	35.8 (32.2 to 39.8)	0.144
Income (<US\$40 000), N (%)	441 (25.3)	154 (35.2)	121 (27.8)	89 (20.4)	77 (17.6)	<0.001
Education level (>16 years), N (%)	788 (45.1)	182 (41.6)	183 (42.0)	207 (47.5)	216 (49.4)	0.053
Employed, N (%)	1151 (65.9)	239 (54.7)	281 (64.4)	303 (69.5)	328 (75.1)	<0.001
Alcohol consumption, oz/week	0 (0,5.8)	0 (0,5.0)	0 (0,6.5)	0 (0,5.0)	0 (0,12.0)	0.001
Current smoking, N (%)	68 (3.9)	26 (5.9)	17 (3.9)	10 (2.3)	15 (3.4)	0.030
Diabetes duration, years	5.0 (2.0 to 10.0)	5.0 (2.0 to 10.0)	5 (2.0 to 10.0)	5.0 (2.0 to 9.0)	5.0 (2.0 to 9.0)	0.285
Family history of diabetes, N (%)	1112 (63.7)	266 (60.9)	289 (66.3)	272 (62.4)	285 (65.2)	0.316
Fasting glucose, mg/dL	144.0 (122.0 to 174.0)	144.0 (122.0 to 173.0)	145.5 (122.0 to 178.2)	141.5 (120.8 to 172.0)	144.0 (121.0 to 172.0)	0.604
Haemoglobin A1c, %	7.1 (6.5 to 7.9)	7.1 (6.6 to 7.9)	7.1 (6.4 to 7.9)	7.1 (6.4 to 7.8)	7.0 (6.5 to 7.9)	0.642
Estimated glomerular filtration rate, mL/min/1.73 m <sup>2</sup>	93.2 (80.7 to 101.4)	91.6 (79.0 to 99.7)	93.1 (80.7 to 101.0)	93.6 (81.4 to 101.9)	95.1 (82.0 to 102.1)	0.008
Urinary albumin-to-creatinine ratio, mg/g	8.0 (5.0 to 17.0)	9.0 (6.0 to 19.0)	9.0 (5.0 to 21.0)	8.0 (5.0 to 15.0)	8.0 (5.0 to 15.0)	0.003
Cumulative average MVPA, min/week						
Total MVPA	328.8 (220.3 to 469.2)	163.6 (123.1 to 194.2)	267.7 (244.8 to 296.1)	390.1 (356.2 to 426.7)	582.7 (511.9 to 681.6)	<0.001
MVPA in bouts <10 min	266.8 (186.7 to 377.6)	145.2 (105.0 to 174.4)	237.2 (209.9 to 265.7)	324.6 (282.0 to 371.4)	458.3 (383.0 to 534.2)	<0.001
MVPA in bouts ≥10 min	40.6 (10.3 to 99.2)	7.0 (0 to 24.3)	28.0 (7.9 to 57.8)	58.2 (27.1 to 108.4)	130.2 (67.5 to 212.5)	<0.001
4-year change in MVPA, min/week†						
Total MVPA	-54.8 (-198.3 to 63.2)	-42.0 (-116.0 to 22.9)	-57.5 (-193.6 to 50.2)	-73.2 (-236.6 to 81.3)	-53.6 (-248.2 to 120.7)	0.462
MVPA in bouts <10 min	-52.6 (-164.0 to 45.8)	-42.2 (-105.6 to 22.7)	-56.3 (-154 to 28.8)	-65.2 (-222.6 to 59.8)	-59.2 (-221.1 to 85.4)	0.272
MVPA in bouts ≥10 min	0.0 (-45.5 to 32.4)	0.0 (-16.8 to 2.6)	0.0 (-42 to 21.4)	-6.2 (-56.5 to 44.3)	-8.0 (-101.0 to 92.2)	0.799

\*Variables were presented as mean (SD) for normally distributed continuous variables and medians (IQR) for non-normally distributed continuous variables, and as proportions for categorical variables, accordingly.

†The sample was restricted to participants who had accelerometry data at baseline and year 4 and did not occur outcome before year 4 (n=1237).

We first assessed the longitudinal association of objectively measured PA with progression to CKD. In the analysis, PA values were presented as the cumulative average values of all PA (including baseline, year 1, year 4 and year 8/9) measured before the date of the occurrence of outcome or the end of follow-up. The follow-up person-time for each participant was calculated from randomisation to the occurrence of outcome or the last available visit, whichever came first. The incidence rate of outcomes, expressed as per 100 person-years, was calculated as the number of participants occurring progression to CKD divided by the person-years of follow-up. Restricted cubic spline Cox regression was performed to test for linearity of the association of PA with outcome. Cox proportional hazards models were fitted to examine the association between cumulative average values of PA and progression to CKD, without and with adjustments for baseline covariates including age, sex, race, treatment group, BMI, duration of diabetes, family history of diabetes, education, employment status, family income, smoking status, alcohol consumption, fasting glucose, haemoglobin A1c (HbA1c), eGFR and UACR. The proportional hazards assumption was checked using the Schoenfeld residuals, and no violation was found. To further test the effect of bout length, the association of MVPA accumulated in bouts of <10 min or ≥10 min with progression to CKD was performed using the same strategy.

Then, we evaluated the association of average value and longitudinal change (MVPA at year 4 minus that at baseline) of MVPA (total MVPA, MVPA accumulated in bouts of <10 min or ≥10 min) between baseline and year 4 with

progression to CKD, using Cox proportional hazards models adjusted for all aforementioned covariates. For Cox model of longitudinal change in MVPA, total MVPA at baseline was also added as a covariate. For the analyses, to ensure proper temporal associations, participants with outcome occurring before year 4 were excluded and the follow-up person-time was calculated from year 4 through the occurrence of outcome or the last available visit.

As additional exploratory analyses, possible modifications of the association of cumulative average values of total MVPA and 4-year change in total MVPA with progression to CKD were also assessed for the following variables: age (<60 or ≥60 years), sex (females or males), race (white or non-white), treatment group (ILI or DSE), BMI (<30 or ≥30 kg/m<sup>2</sup>) and UACR (<30 or ≥30 mg/g).

A series of sensitivity analyses were performed to assess robustness of results. First, we assessed the association between total MVPA and progression to CKD using the most recent measurement of MVPA. Second, we assessed the association of cumulative average values of total MVPA with outcome with follow-up time starting from the date of the last MVPA measurement. Third, we also evaluated the association of average values of total MVPA at baseline and year 1, as well as 1-year change in total MVPA (MVPA at year 1 minus that at baseline), with progression to CKD occurring after 1 year. Fourth, the outcome was redefined as eGFR<60 mL/min per 1.73 m<sup>2</sup> with at least 40% drop or end-stage renal disease, and the association of cumulative average values of total MVPA and 4-year change in total MVPA with the outcome was evaluated. Fifth, we further adjusted for average weight during follow-up in the analysis of

cumulative average values of MVPA, as well as 4-year change in weight in the analysis of 4-year change in MVPA. Sixth, we reassessed the association of total MVPA and progression to CKD using the second or third quartiles as a reference. Seventh, in the Look AHEAD trial, the first 50% of participants were invited to complete a semi-quantitative food frequency questionnaire to assess dietary intake. Among this subsample, we further adjusted for dietary factors. Eighth, cumulative average values of covariables (BMI, fasting glucose, HbA1c, eGFR and UACR) or 4-year change in covariables were adjusted for accordingly.

A two-tailed  $p < 0.05$  was considered to be statistically significant in all analyses. Analyses were performed using R V.4.1.1 software (<http://www.R-project.org/>).

### Patient and public involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

### Equity, diversity and inclusion statement

Our research team included eight women and two men from Asia and all authors are at the early-stage or mid-stage of their careers. The Look AHEAD trial sample was population-based (including a broad range of socio-demographic characteristics), but not population-representative. At recruitment, the Look AHEAD trial endeavoured to recruit approximately equal numbers of men and women and to recruit a minimum of 33% from racial and ethnic minority groups including African Americans, Hispanic Americans, American Indians and Asian Americans.

## RESULTS

### Study participants and population characteristics

Of the 1746 participants included, the mean age was 58.7 (SD, 6.8) years, and 1025 (58.7%) were women. 1563 (89.5%) of participants had at least two MVPA measurements (online supplemental table 1). The median (IQR) time spent in total MVPA, MVPA accumulated in bouts of  $<10$  min and MVPA accumulated in bouts of  $\geq 10$  min was 328.8 (220.3 to 469.2), 266.8 (186.7 to 377.6) and 40.6 (10.3 to 99.2) min/week, respectively (online supplemental table 1).

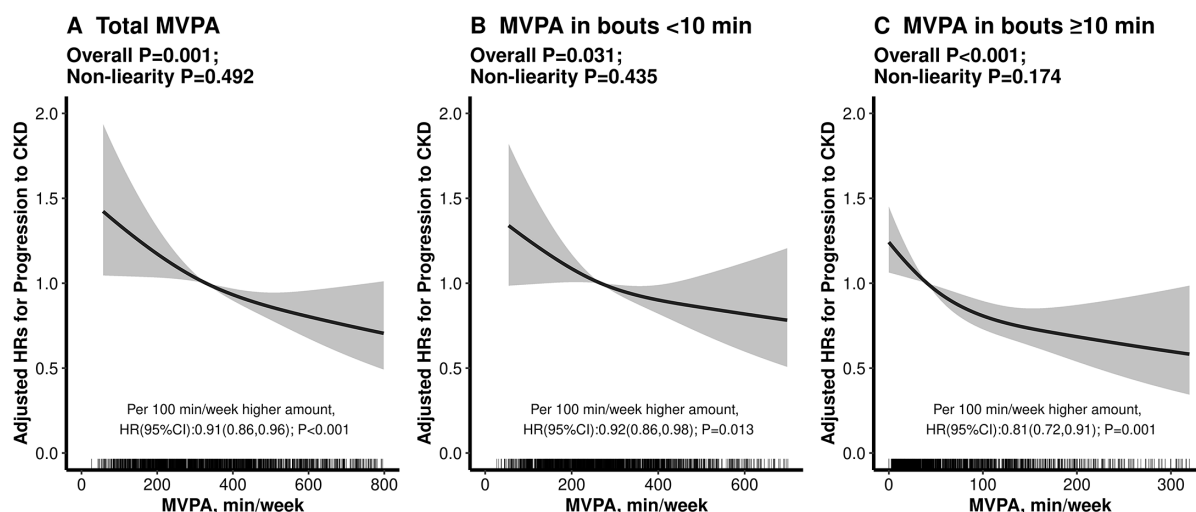
As shown in table 1, compared with participants with lower total MVPA, those with higher MVPA were younger, more likely to be men and employed and tended to have higher income level and better renal function at baseline.

### Association between cumulative average values of MVPA and the risk of progression to CKD

During a median follow-up of 12.0 years (IQR, 7.9 to 16.0 years), 567 (32.5%) participants experienced progression to CKD. All outcomes were defined by eGFR measurement, except for two cases identified by self-reported kidney failure.

Overall, there was a linear association of total MVPA with progression to CKD (per 100 min/week higher amount, HR: 0.91; 95% CI: 0.86 to 0.96; overall  $p=0.001$ ;  $p$  for non-linearity=0.492; figure 1). Consistently, when total MVPA was assessed as quartiles, a significantly lower risk of progression to CKD was found in participants in the third (328.8 to  $<469.2$  min/week; HR: 0.73; 95% CI: 0.57 to 0.93) and fourth ( $\geq 469.2$  min/week; HR: 0.69; 95% CI: 0.53 to 0.89) quartiles, compared with those in the first quartile ( $<220.3$  min/week) (table 2). As expected, there was an inverse association of total volume of PA and intensity-special PA (LPA, MPA and VPA) with progression to CKD, while a positive association of SED with progression to CKD (online supplemental table 2). Nevertheless, the association for SED and LPA were attenuated and tended toward null after further adjusting for MPA and VPA, while the inverse association for MVPA did not change substantially after further adjusting for SED and LPA (online supplemental table 2).

When considering the pattern of MVPA accumulation, an inverse association was observed for MVPA accumulated in bouts of both  $<10$  min and  $\geq 10$  min (figure 1 and table 2). However, after mutually adjusting for MVPA accumulated in bouts of  $<10$  min and  $\geq 10$  min, the inverse association for MVPA accumulated in bouts of  $\geq 10$  min did not change substantially, while the association for MVPA accumulated in bouts of  $<10$  min was attenuated and no longer significant (online supplemental table 3).



**Figure 1** The association of moderate-to-vigorous physical activity (cumulative average value) and the risk of progression to chronic kidney disease (CKD) based on restricted cubic splines (N=1746). \*Adjusted for age, sex, race, treatment group, body mass index, duration of diabetes, family history of diabetes, education, employment status, family income, smoking status, alcohol consumption, fasting glucose, haemoglobin A1c, estimated glomerular filtration rate and urinary albumin-to-creatinine ratio at baseline. MVPA, moderate-to-vigorous physical activity.



**Table 2** The association of moderate-to-vigorous physical activity (cumulative average value) with the risk of progression to chronic kidney disease (CKD) (N=1746)

		Cases	Adjusted model 1†		Adjusted model 2†	
	N	(incidence rate*)	HR (95% CI)	P value	HR (95% CI)	P value
Total MVPA, min/week						
Quartiles						
Q1 (<220.3)	437	159 (3.6)	Ref		Ref	
Q2 (220.3 to <328.8)	436	157 (3.2)	1.01 (0.80 to 1.26)	0.957	0.98 (0.78 to 1.23)	0.851
Q3 (328.8 to <469.2)	436	130 (2.5)	0.74 (0.58 to 0.95)	0.016	0.73 (0.57 to 0.93)	0.010
Q4 (≥469.2)	437	121 (2.3)	0.70 (0.54 to 0.90)	0.006	0.69 (0.53 to 0.89)	0.004
P for trend			0.001		0.001	
MVPA in bouts <10 min, min/week						
Quartiles						
Q1 (<186.7)	435	156 (3.5)	Ref		Ref	
Q2 (186.7 to <266.7)	438	156 (3.2)	1.02 (0.82 to 1.28)	0.845	1.04 (0.83 to 1.31)	0.724
Q3 (266.7 to <377.6)	436	132 (2.5)	0.79 (0.62 to 1.01)	0.058	0.74 (0.58 to 0.95)	0.018
Q4 (≥377.6)	437	123 (2.3)	0.83 (0.64 to 1.07)	0.144	0.78 (0.60 to 1.02)	0.066
P for trend			0.041		0.010	
MVPA in bouts ≥10 min, min/week						
Quartiles						
Q1 (<10.3)	437	159 (3.6)	Ref		Ref	
Q2 (10.3 to <40.6)	436	155 (3.1)	0.86 (0.69 to 1.08)	0.193	0.84 (0.67 to 1.06)	0.145
Q3 (40.6 to <99.2)	436	125 (2.4)	0.65 (0.51 to 0.83)	0.001	0.66 (0.52 to 0.85)	0.001
Q4 (≥99.2)	437	128 (2.3)	0.57 (0.45 to 0.73)	<0.001	0.60 (0.47 to 0.77)	<0.001
P for trend			<0.001		<0.001	

\*Incidence rates were presented as per 100 person-years.

†Model 1 adjusted for age, sex, race and treatment group. Model 2 further adjusted for body mass index, duration of diabetes, family history of diabetes, education, employment status, family income, smoking status, alcohol consumption, fasting glucose, haemoglobin A1c, estimated glomerular filtration rate and urinary albumin-to-creatinine ratio at baseline.

MVPA, moderate-to-vigorous physical activity.

### Association of 4-year change in MVPA with the risk of progression to CKD

Among 1237 participants who had accelerometry data at both baseline and year 4 and did not occur outcome before year 4, 376 (30.4%) participants experienced progression to CKD.

The median (IQR) time of average value of total MVPA at baseline and year 4 was 324.1 (218.5 to 461.5) min/week. Similarly, there was an inverse association between 4-year average value of MVPA and progression to CKD (table 3).

The median (IQR) time of 4-year change in total MVPA was −54.8 (−198.3 to 63.2) min/week, and 783 (63.3%) participants had a reduction in MVPA time at year 4. When the 4-year change in MVPA was assessed as quartiles, compared with the largest MVPA reduction (the first quartile of 4-year change in MVPA, <−198.3 min/week), an increase in total MVPA (the fourth quartile, ≥63.2 min/week) was associated with a 33% lower risk of progression to CKD (HR: 0.67; 95% CI: 0.47 to 0.97; table 3). A lower risk of progression to CKD was also observed for an increase in MVPA accumulated in bouts of both <10 min and ≥10 min, even with mutually adjustment for MVPA accumulated in bouts of <10 min and ≥10 min (table 3 and online supplemental table 3).

### Stratified analyses and sensitivity analyses

Stratified analyses were performed to further assess the association of cumulative average values of total MVPA and 4-year change in total MVPA with progression to CKD in various subgroups (online supplemental table 4). None of the variables, including age, sex, BMI, race, treatment group and UACR showed significant effect modifications on the association.

For sensitivity analyses, the results did not change substantially using the most recent measurement of total MVPA (Sensitivity analysis 1), or starting follow-up time from the date of the last MVPA measurement (Sensitivity analysis 2) (online supplemental table 5). Moreover, 1-year average values and change of total MVPA at baseline and year 1 were also inversely associated with outcome that occurred after the first year (Sensitivity analysis 3) (online supplemental table 5). Finally, the results did not change substantially after redefining the outcome as eGFR<60 mL/min per 1.73 m<sup>2</sup> with at least 40% drop or end-stage renal disease (Sensitivity analysis 4), further adjusting for average weight during follow-up or 4-year change in weight (Sensitivity analysis 5), using the second or third quartiles as a reference (Sensitivity analysis 6), further adjusting for dietary factors (Sensitivity analysis 7) or considering covariables (BMI, fasting glucose, HbA1c, eGFR and UACR) during follow-up (Sensitivity analysis 8) (online supplemental table 5).

### DISCUSSION

In this secondary analysis of the Look AHEAD trial, we first demonstrated that both a longer mean duration of MVPA, and an increase of MVPA duration during follow-up were associated with a lower risk of progression to CKD among patients with overweight/obesity and T2D. A lower risk of progression to CKD was observed for an increase in MVPA accumulated in bouts of both <10 min and ≥10 min.

Our study provides novel evidence regarding the association of objectively measured MVPA with renal health. Most of the previous studies<sup>5–9</sup> only evaluated the short-term qualitative effect of self-reported PA at baseline on renal outcomes among

**Table 3** The association of mean and longitudinal change of moderate-to-vigorous physical activity (MVPA) between baseline and year 4 with the risk of progression to chronic kidney disease (N=1237)

	Total MVPA			MVPA in bouts <10 min			MVPA in bouts ≥10 min		
	Cases/N (incidence rate)*	Adjusted HR (95% CI)†	P value	Cases/N (incidence rate)*	Adjusted HR (95% CI)†	P value	Cases/N (incidence rate)*	Adjusted HR (95% CI)†	P value
4-year average value of MVPA									
Quartile‡									
Q1	105/309 (4.4)	Ref		107/309 (4.4)	Ref		102/305 (4.0)	Ref	
Q2	111/309 (4.1)	0.98 (0.74 to 1.30)	0.893	103/309 (3.8)	0.96 (0.73 to 1.27)	0.773	96/313 (3.6)	0.89 (0.67 to 1.19)	0.429
Q3	81/309 (2.8)	0.71 (0.52 to 0.97)	0.029	85/307 (3.0)	0.76 (0.56 to 1.03)	0.072	93/309 (3.4)	0.86 (0.64 to 1.16)	0.321
Q4	79/310 (2.6)	0.61 (0.44 to 0.84)	0.003	81/312 (2.7)	0.64 (0.47 to 0.88)	0.006	85/310 (2.8)	0.65 (0.47 to 0.89)	0.008
P for trend	<0.001			0.002			0.009		
4-year longitudinal change of MVPA									
Quartile‡									
Q1	94/308 (3.5)	Ref		92/308 (3.4)	Ref		98/309 (3.6)	Ref	
Q2	89/309 (3.3)	0.80 (0.58 to 1.11)	0.179	96/310 (3.5)	0.80 (0.58 to 1.10)	0.164	83/262 (3.6)	0.90 (0.66 to 1.23)	0.526
Q3	107/310 (4.0)	0.89 (0.63 to 1.26)	0.520	103/309 (3.7)	0.79 (0.57 to 1.10)	0.167	111/356 (3.6)	0.82 (0.59 to 1.13)	0.222
Q4	86/310 (3.0)	0.67 (0.47 to 0.97)	0.033	85/310 (3.0)	0.67 (0.48 to 0.96)	0.028	84/310 (2.9)	0.71 (0.51 to 0.98)	0.036
P for trend	0.066			0.043			0.030		
*The analyses were restricted to participants who had accelerometry data at baseline and year 4 and did not occur outcome before year 4 (n=1237); incidence rates were presented as per 100 person-years.									
†Adjusted for age, sex, race, treatment group, body mass index, duration of diabetes, family history of diabetes, education, employment status, family income, smoking status, alcohol consumption, fasting glucose, haemoglobin A1c, estimated glomerular filtration rate and urinary albumin-to-creatinine ratio at baseline. For 4-year change in MVPA, total moderate-to-vigorous physical activity at baseline was also adjusted for.									
‡Quartiles of 4-year average value in MVPA (min/week): Q1: <218.5; Q2: 218.5 to <324.1; Q3: 324.1 to <461.5; Q4: ≥461.5 for total MVPA; Q1: <181.5; Q2: 181.5 to <270.4; Q3: 270.4 to <365.8; Q4: ≥365.8 for MVPA in bouts <10 min; Q1: <10.5; Q2: 10.5 to <41.4; Q3: 41.4 to <99.7; Q4: ≥99.7 for MVPA in bouts ≥10 min; quartiles of 4-year change in MVPA (min/week): Q1: <-198.3; Q2: -198.3 to <-54.8; Q3: -54.8 to <63.2; Q4: ≥63.2 for total MVPA; Q1: <-164.0; Q2: -164.0 to <-52.6; Q3: -52.6 to <45.8; Q4: ≥45.8 for MVPA in bouts <10 min; Q1: <-45.5; Q2: -45.5 to <0; Q3: 0 to <32.4; Q4: ≥32.4 for MVPA in bouts ≥10 min.									

patients with T2D. Prior to this study, only one small-scale study (n=326) has examined the association between accelerometry-measured PA and kidney function in patients with recently diagnosed T2D,<sup>10</sup> and found no significant association between 4-year change in MVPA and kidney function at year 4. Of note, the result should be interpreted with caution, given that the study did not consider the effect of renal function at baseline and therefore could not accurately assess its longitudinal association. Thus, prior to this study, the longitudinal association of objectively measured MVPA with progression to CKD among patients with T2D was unclear. Based on repeated objective measures of unsupervised PA and the long-term follow-up in a well-characterised cohort, our study showed a significant inverse association between MVPA and progression to CKD among patients with overweight/obesity and T2D. These findings are consistent with evidence that regular PA has direct anti-inflammatory effects,<sup>28–29</sup> and can promote glycaemic control, improve insulin sensitivity, blood pressure, lipid profiles and other metabolic and cardiovascular risk factors,<sup>28–31</sup> all of which are associated with renal function. Furthermore, the association between MVPA and progression to CKD was nearly linear, without an observable plateau or a clear threshold, suggesting that people with diabetes should be encouraged to engage in as much MVPA as they can tolerate to maximise the benefits. Of note, the average MVPA time in the current study was higher than that in US adults with diabetes (averaged approximately 86 min/week MVPA).<sup>32–33</sup> This may be partially explained by the fact that all Look AHEAD participants had to pass a maximal exercise test at baseline, and individuals with a fitness level of <4 METs were excluded from the study.<sup>34</sup> Furthermore, eligible Look AHEAD participants were randomly assigned to either diabetes support and education or lifestyle intervention, both of

which may increase their MVPA levels. At the same time, differences in the accelerometer or accelerometer cut-points may also partly account for these observed differences in MVPA time.<sup>34</sup>

Moreover, compared with longitudinal decrease in MVPA, an increase in accelerometry-measured MVPA was associated with a lower risk of subsequent progression to CKD among people with overweight/obesity and T2D. Similar inverse association was found for both 1-year and 4-year change in MVPA. These results indicate that maintaining appropriate MVPA duration or some increase may have a more favourable impact on renal outcomes in people with T2D.

Another unique contribution of this study was the results for MVPA accumulated in bouts of <10 min and ≥10 min. Little is known about whether bout length of MVPA influences its association with renal health,<sup>14</sup> which is important given that a short bout of MVPA may be more feasible and acceptable than a bout of ≥10 min for people with diabetes who have low PA levels and spend limited time in MVPA.<sup>35</sup> Indeed, we observed that the majority of MVPA occurred in bouts <10 min. Furthermore, MVPA accumulated in bouts of <10 min was at a higher level, with 85.3% of the participants meeting current guideline recommendations, which may partly explain the null association for average time of MVPA accumulated in bouts of <10 min with study outcome, suggesting that further increases in short-bout MVPA may not be sufficient to further improve renal health in people with adequate levels of short bouts of MVPA. However, we did observe that a longitudinal increase in short bouts of MVPA was significantly associated with a reduced risk of progression to CKD, compared with a decrease in short bouts of MVPA, independent of change in long bouts of MVPA, suggesting that maintaining a high level of short bouts of MVPA may also be important for renal health and supporting the recent

changes to policy in the USA and WHO guidelines that have removed the suggestion that MVPA should be accumulated in bouts of at least 10 min.<sup>12 13</sup> The renal benefit of short bouts of MVPA is biologically plausible given that a single bout of PA can reduce insulin resistance and increase insulin sensitivity by facilitating movement of glucose across the cellular membrane via both insulin dependent and insulin independent glucose transporter type 4 (GLUT-4) transporters.<sup>36</sup>

### Clinical implications

Our study has important public health implications because it suggests that maintaining a high level of MVPA, regardless of length of the bout, may have renal benefit for adults with overweight/obesity and T2D, especially for individuals who are unwilling or unable to engage in PA bouts that are  $\geq 10$  min in duration. To reduce risk of progression to CKD, an adult with overweight/obesity and T2D could take 67 min moderate activity 7 days of the week, such as brisk walk, slow cycling, jogging, slow sweeping, slow swimming and so on, to reach 469 min/week (the 75th percentile) of MVPA.

### Limitations

First, the findings are based on secondary data analyses that are not based on the randomised design, which may introduce selection bias and unmeasured confounding. Moreover, reverse causation is possible due to the observational nature of the study, and thus, causality cannot be determined from our findings. Second, this study included a subsample of the full Look AHEAD cohort who participated in the accelerometry substudy and provided sufficient data for analysis. However, there were similar demographic characteristics between participants with valid baseline accelerometry data and the total Look AHEAD study sample except for race ethnicity,<sup>19</sup> and stratified analyses showed similar results across race. Moreover, the participants in our study were a very motivated population due to their participation in a trial that had a lifestyle intervention, which may be not representative of most people with diabetes and obesity. Therefore, it is important to validate our findings in other adults with overweight/obesity and T2D. Third, accelerometers that primarily measure locomotor activity may not be sensitive to detecting upper body movement and may not accurately assess activities that require more energy per movement (eg, carrying loads and travelling up an incline), leading to an underestimation of PA. Moreover, PA was assessed over a period of 7 days at each assessment point. However, 7-day monitoring periods have been routinely used because they provide an opportunity to sample PA on both weekdays and weekend days and achieve a greater than 80% intra-class correlations in most populations.<sup>37</sup> Fourth, the RT3 accelerometer is not commonly used in PA research and the processing methods of the raw accelerometer data is proprietary, which limits comparability to other studies. Moreover, a 1 min epoch was used due to technical constraints, which limits the interpretation of the results related to the importance of the bout criterion and a shorter epoch length could retain more information.

### CONCLUSIONS

In summary, in the secondary analyses of the Look AHEAD trial, regardless of length bout of each MVPA, both a longer duration of MVPA, and an increase of MVPA duration during follow-up

were associated with a reduced risk of progression to CKD in adults with overweight/obesity and T2D.

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