Journal of Diabetes and Its Complications 39 (2025) 109065

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.elsevier.com/locate/jdiacomp

Research paper

Physical activity and albuminuria in individuals recently diagnosed with type 2 diabetes

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ARTICLE INFO

Keywords:
Accelerometer
Albuminuria
Physical activity
Sedentary time
Type 2 diabetes mellitus

ABSTRACT

Aims: We aimed to investigate the association between objectively measured physical activity and the presence and development of albuminuria in individuals recently diagnosed with type 2 diabetes at baseline.
Methods: This study was based on data from The Danish Centre for Strategic Research in Type 2 diabetes cohort (N = 832). We assessed moderate to vigorous physical activity (MVPA) and sedentary time by 24-hour dual-monitor accelerometry at baseline and 4-years follow-up and investigated the association with albuminuria, defined as urine albumin/creatinine-ratio (UACR) ≥30 mg/g, measured from a urine sample. The odds ratio (OR) for the presence and development of albuminuria were investigated using multiple logistic regressions.
Results: We found an inverse association between baseline MVPA and both presence (OR: 0.82; 95 % CI: 0.69–0.98) and incidence of albuminuria (OR: 0.74; 95 % CI: 0.59–0.94), independent of known confounding factors. However, sedentary time was not significantly associated with increased development of albuminuria. Moreover, neither decrease in MVPA (OR: 0.79; 95 % CI: 0.42–1.49) nor increase in sedentary time (OR: 1.03; 95 % CI: 0.98–1.09) were significantly associated with development of albuminuria from baseline to 4-years follow-up.
Conclusions: Our findings demonstrate an inverse association between baseline MVPA and development of albuminuria in individuals recently diagnosed with type 2 diabetes. An increase in MVPA from baseline to follow-up inferred 21 % lower incidence of albuminuria after 4-years follow-up, albeit insignificant, likely due to the relatively small sample size at follow-up and the lack of larger changes in physical activity.
Clinical trial registration number: NCT02015130

1. Introduction

Non-communicable diseases, including type 2 diabetes, are a major challenge for global health.[1] The prevalence of diabetes is increasing, and it is now affecting approximately 10 % of the World's population.[2] In a systematic review, diabetes was shown to be the leading cause of chronic kidney disease (CKD), accounting for 30–50 % of all cases,[3] and since diabetes with CKD is associated with a 7-fold absolute risk of all-cause mortality compared to diabetes without CKD,[4] it is an important health issue to address.

It has previously been demonstrated that individuals with type 2 diabetes are less physically active than individuals without a chronic disease.[5] Physical activity has previously been shown to both improve traditional intermediating cardiovascular risk factors, and have an additional effect beyond that, through e.g. reduced chronic low-grade inflammation, and improved cardiorespiratory fitness and muscular strength, which have beneficial effects in patients with CKD.[6–10]

Several cross-sectional studies have shown that the risk of albuminuria and CKD was lower among physically active individuals in the general population,[11–14] yet no causal relationship can be deduced

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https://doi.org/10.1016/j.jdiacomp.2025.109065
Received 19 December 2024; Received in revised form 12 April 2025; Accepted 3 May 2025
Available online 13 May 2025

therefrom. One longitudinal study[15] and a systematic review[16] have likewise shown an inverse association between physical activity and albuminuria, however, these studies have not been conducted exclusively in participants with type 2 diabetes.

Two prospective studies, conducted exclusively in individuals with type 2 diabetes, have shown an inverse association between physical activity and progression of renal dysfunction or albuminuria,[17,18] yet these studies relied on self-reported physical activity, which is prone to recall bias.[19] To the best of our knowledge, only one former study has examined the association between objectively measured physical activity and development of albuminuria in individuals with type 2 diabetes. This study showed an inverse association between changes in physical activity and serum creatinine, but no significant association with changes in either eGFR or albuminuria in 4-years follow-up.[20] However, the study only examined how change in physical activity affected kidney function, and it did not take baseline physical activity into account.

Therefore, this study aimed to investigate the association between objectively measured physical activity and the presence and development of albuminuria in individuals recently diagnosed with type 2 diabetes at baseline.

2. Subjects, materials and methods

2.1. Participants

This study was based on data from The Specialist Supervised Individualized Treatment of New Clinically Diagnosed Type 2 Diabetes in General Practice (IDA),[21] which is an ongoing prospective, controlled, multicenter intervention study nested in The Danish Centre for Strategic Research in Type 2 diabetes cohort (DD2).[22] All participants were recently diagnosed with type 2 diabetes at baseline according to criteria defined in DD2. The median diabetes duration at time of IDA enrollment was 3.5 years (Interquartile interval (IQI): 0.9 years, 5.6 years). The inclusion criteria in IDA study can be found elsewhere.[21] Baseline examinations were conducted between 2013 and 2018 at four centers across Denmark.

In total, 1172 individuals gave their written, informed consent to participate in IDA, of which 881 had valid accelerometer data at baseline (see below). Of these, 832 participants also had clinical measurements of urine albumin/creatinine-ratio (UACR) at baseline, and 659 at 4-years follow-up. The accelerometer measurements were repeated in 459 of the original 881 participants at 4-years follow-up. Of the 459 participants with valid accelerometer data at both baseline and 4-years follow-up, 337 participants also had their UACR measured at both baseline and 4-years follow-up.

This study was based on participants in the IDA study,[21] which has been approved by the Regional Committee on Medical Health Ethics (Region of Southern Denmark S-20120186), the Danish Data Protection Agency and Medicines Authority (journal no. 2012120204). The study was conducted in concordance with the Helsinki declaration II.

The present article was written following the STROBE-guidelines.

2.2. UACR

Information on UACR was obtained from a urine sample at the clinical examination closest to examinations at enrollment and 4-years follow-up. UACR was both assessed as a dichotomous variable, defined as <30 mg/g or ≥ 30 mg/g and as a categorical ordinal variable with three categories: <30 mg/g, 30–300 mg/g and ≥ 300 mg/g. Albuminuria was defined as UACR ≥ 30 mg/g and macroalbuminuria was defined as UACR ≥ 300 mg/g.

2.3. Physical activity

Physical activity, including sedentary time and intensity, was assessed by 24-hour dual-monitor accelerometry worn for 10 consecutive days at baseline and follow-up. Two tri-axial accelerometers (Axivity AX3, Axivity, Newcastle, UK) were attached directly on the skin; one on the lower back and another on the right thigh. Inclusion criteria for valid physical activity registration were 1) >22 h of daily wear time, 2) >2 weekdays (Mon-Fri) and 3) >1 weekend day (Sat-Sun). More detailed information of the accelerometer-based measurement of physical activity can be found elsewhere.[23]

Physical activity intensities were categorized using ActiGraph counts generated from raw acceleration measured at the back using an epoch length of 10 s.[24] Sedentary time was defined as <100 cpm[25] and was both assessed as a continuous numerical variable as daily time spent sedentary and as a dichotomous variable, where participants were categorized into high sedentary time (above the median) or low sedentary time (at/below the median). Moderate physical activity was determined by the average counts at preferred walking speed, while vigorous activity was determined by the average counts at running equivalent to 60 % of VO_2max – both based on age-specific cut points,[23] determined in an internally conducted calibration study using established methods.[26] Moderate and vigorous physical activity (MVPA) were combined in the analyses and assessed both as a continuous numerical variable as daily time spent in MVPA and as a dichotomous variable, where participants were divided into high/low MVPA depending on whether or not they met the recommendation of 30 min of daily MVPA according to the Danish Health Authorities.[27]

2.4. Measures of variables

The fasting blood sample from the DD2 enrollment was used to measure serum C-peptide and plasma glucose as well as estimate fasting derived indices of insulin resistance (HOMA2IR) and beta-cell function (HOMA2B) using the homeostasis model assessment-2 (HOMA2) computational model (University of Oxford, Oxford, U.K.).[21,28] Information on LDL-cholesterol, HbA1c and estimated glomerular filtration rate (eGFR) were obtained from the clinical examinations closest to examinations at enrollment and 4-years follow-up.

Automated office blood pressure was measured using oscillometric techniques by Mobil-O-graph PWA (IEM GmbH, Stolberg, Germany). Patients were left unobserved in sitting position and blood pressure (BP) was measured 3 min apart for 30 min. Mean values of systolic- and diastolic BP were reported.

Medical history regarding medication (glucose-, BP-, lipid-lowering and kidney-protective medication) and co-morbidity (cancer and CVD) was gathered by patient interview at baseline and 4-years follow-up and verified by hospital charts and Shared Medication Records. Kidney-protective medication was defined as sodium-glucose cotransporter-2 (SGLT-2)-inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, angiotensin converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARB) and mineralocorticoid receptor antagonists (ARA), since these have previously been shown to preserve kidney function and/or to decrease UACR.[29–31]

CVD was defined as previous myocardial infarction, coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), stroke, other arterial revascularization procedures, amputation due to macrovascular insufficiency or ankle-brachial pressure index of <0.9. Smoking habits and alcohol use were collected by patient questionnaires at baseline.

2.5. Statistics

Baseline characteristics of the participants are displayed as medians with interquartile intervals (IQI) and compared using the Kruskal-Wallis test, or as numbers with percentages and compared using the chi-squared test. Associations between physical activity and UACR were investigated using logistic regression, with results presented as odds ratios (ORs) with 95 % confidence intervals (CI). To make results more

Table 1
Baseline characteristics stratified by moderate to vigorous physical activity (MVPA) and sedentary time (ST) in 881 individuals recently diagnosed with type 2 diabetes.

	MVPA < 30 min/day	MVPA ≥ 30 min/day	*p*-Value	ST below median (609 min/day)	ST above median (609 min/day)	*p*-Value
n	762 (86.5)	119 (13.5)		440 (49.9)	441 (50.1)	
Sex (female)	322 (42.3)	40 (33.6)	0.07	194 (44.1)	168 (38.1)	0.07
Age (years)	62.1 (54.0; 69.0)	59.9 (51.0; 66.2)	0.02	59.9 (52.2; 66.8)	63.8 (55.9; 69.6)	0.00
BMI (kg/m^2)	31.6 (28.3; 35.5)	28.0 (25.5; 31.0)	0.00	30.4 (27.5; 34.1)	31.8 (28.2; 35.9)	0.00
Smoke						
Never smoke	310 (40.7)	56 (47.1)		186 (42.3)	180 (40.8)	
Current smoker	149 (19.6)	10 (8.4)		78 (17.7)	81 (18.4)	
Former smoker	303 (39.8)	53 (44.5)	0.01	176 (40.0)	180 (40.8)	0.91
Alcohol consumption						
Above 7–14/week*	141 (18.5)	25 (21.0)	0.52	83 (18.9)	83 (18.8)	0.99
HbA1c (mmol/l)	49 (45; 55)	49 (45; 55)		49 (45; 54)	49 (45; 56)	
HbA1c (%)	6.6 (6.3; 7.2)	6.6 (6.3; 7.2)	0.79	6.6 (6.3; 7.1)	6.5 (6.3; 7.3)	0.88
Fasting plasma glucose (mmol/l)	7.63 (6.72; 8.89)	7.55 (6.55; 8.65)	0.43	7.67 (6.74; 8.93)	7.56 (6.63; 8.76)	0.26
Fasting C-peptide (pmol/l)	1185 (906; 1569)	990 (711; 1256)	0.00	1121 (867; 1489)	1168 (891; 1574)	0.27
HOMA2B (%)	86.1 (63.9; 112.6)	76.3 (56.6; 102.2)	0.00	81.8 (61.2; 108.7)	87.6 (62.6; 113.2)	0.14
HOMA2IR (%)	3.0 (2.3; 4.0)	2.4 (1.7; 3.1)	0.00	2.9 (2.2; 3.8)	3.0 (2.2; 4.1)	0.32
Systolic BP (mmHg)	129 (121; 138)	127 (118; 136)	0.03	128 (120; 137)	129 (120; 138)	0.85
Diastolic BP (mmHg)	82 (75; 88)	82 (76; 89)	0.87	83 (76; 89)	81 (74; 88)	0.01
LDL-cholesterol (mmol/l)	2.1 (1.7; 2.7)	2.1 (1.6; 2.8)	0.64	2.1 (1.6; 2.7)	2.1 (1.7; 2.6)	0.82
eGFR						
<60 mL/min/1.73 m^2	48 (6.3)	6 (5.0)		21 (4.8)	33 (7.5)	
≥60 mL/min/1.73 m^2	714 (93.7)	113 (95.0)	0.59	419 (95.2)	408 (92.5)	0.09
Cancer (yes)	81 (10.6)	8 (6.7)	0.19	37 (8.4)	52 (11.8)	0.10
CVD** (yes)	123 (16.1)	14 (11.8)	0.22	61 (13.9)	76 (17.2)	0.17
UACR						
<30 mg/g	601 (83.6)	100 (88.5)		360 (87.2)	341 (81.4)	
30–300 mg/g	105 (14.6)	11 (9.7)		46 (11.1)	70 (16.7)	
>300 mg/g	13 (1.8)	2 (1.8)	0.38	7 (1.7)	8 (1.9)	0.06
Kidney-protective medicine						
None	280 (36.7)	50 (42.0)		183 (41.6)	147 (33.3)	
Monotherapy	425 (55.8)	63 (52.9)		228 (51.8)	260 (59.0)	
Dual therapy	53 (7.0)	6 (5.0)		25 (5.7)	34 (7.7)	
≥3 drugs	4 (0.5)	0 (0.0)	0.55	4 (0.9)	0 (0.0)	0.01
Glucose-lowering drugs						
None	89 (11.7)	14 (11.8)		50 (11.4)	53 (12.0)	
Monotherapy	518 (68.0)	85 (71.4)		303 (68.9)	300 (68.0)	
Dual therapy	130 (17.1)	16 (13.4)		70 (15.9)	76 (17.2)	
≥3 drugs	25 (3.3)	4 (3.4)	0.80	17 (3.9)	12 (2.7)	0.75
BP-lowering drugs						
None	203 (26.6)	45 (37.8)		135 (30.7)	113 (25.6)	
Monotherapy	208 (27.3)	40 (33.6)		135 (30.7)	113 (25.6)	
Dual therapy	183 (24.0)	19 (16.0)		93 (21.1)	109 (24.7)	
≥3 drugs	168 (22.0)	15 (12.6)	0.00	77 (17.5)	106 (24.0)	0.02
Lipid-lowering drugs						
None	191 (25.1)	41 (34.5)		115 (26.1)	117 (26.5)	
Monotherapy	562 (73.8)	76 (63.9)		317 (72.0)	321 (72.8)	
Dual therapy	9 (1.2)	2 (1.7)	0.08	8 (1.8)	3 (0.7)	0.31

Note: Values are medians with interquartile intervals or numbers (%).
Abbreviations: MVPA </≥ 30, time spent in MVPA below or at/above 30 min/day; BMI, Body mass index; BP, Blood pressure; LDL-c, Low density lipoprotein cholesterol; eGFR, Estimated glomerular filtration rate; CVD, Cardiovascular disease; UACR, Urine albumin/creatinine-ratio.
* 7 alcohol units for women and 14 alcohol units for men.
** CVD includes former acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), stroke, amputation due to macrovascular insufficiency, other arterial revascularization procedures or ankle-brachial pressure index of <0.9.

interpretable the ORs were transformed to represent 10 min/day increase in MVPA or 60 min/day increase in sedentary time in both baseline and follow-up analyses.

The cross-sectional association is presented unadjusted (model 1), adjusted for age and sex (model 2) and further adjusted for smoking, alcohol consumption, BMI, LDL-cholesterol, HbA1c, diabetes duration, systolic BP, cardiovascular disease, cancer and baseline use of kidney-protective medication (model 3).

To assess the impact of physical activity levels at baseline on the odds of progressing to albuminuria at 4-years follow-up, the adjustments in model 3 were slightly modified to include changes in kidney-protective medication use (instead of baseline medication) and baseline UACR. The association was further evaluated for interactions with age, sex, smoking, alcohol consumption, change in use of kidney-protective medication, LDL-cholesterol, BMI, systolic- and diastolic BP, HbA1c, CVD and cancer, by adding an interaction term in the fully adjusted logistic regression. Furthermore, the interactions were illustrated in a forest plot, which was carried out in Microsoft Excel 16.78.3.

When investigating the association between change in levels of physical activity from baseline to 4-years follow-up and progression to albuminuria, the adjustments in model 3 further included adjustment for baseline levels of physical activity.

For all logistic regressions, we investigated the assumptions of the model using diagnostic plots to see if the log-odds of the outcome and independent variable had a linear relationship (data not shown). A directed acyclic graph is presented to show the relations between potential confounders (ESM Fig. S1).

To assess the risk of selection bias, we compared baseline characteristics between participants who had UACR measured at both baseline and follow-up and participants who only had it measured at baseline.

Similarly, we compared those who had accelerometer-measured physical activity at both time-points and those who only had it measured at baseline. Sensitivity analyses included assessing the impact of kidney-protective medication by restricting the analysis to individuals with constant kidney-protective medication, and evaluating whether including progression from microalbuminuria to macroalbuminuria altered the risk estimates.

All statistical analyses were carried out in Stata/BE 17.0 (StataCorp LLC, Texas, US), and a *p*-value of 0.05 or below was considered statistically significant.

3. Results

3.1. Baseline characteristics

Among the 881 participants included in this study, 119 individuals (13.5 %) reached an average of 30 min of daily MVPA as recommended by the Danish Health Authorities.[27] Individuals with a high MVPA were younger, and they had a lower BMI, fasting C-peptide, HOMA2B, HOMA2IR and systolic BP compared to individuals with a low MVPA. Moreover, they were less likely to be smokers and to take BP-lowering medication (all $p < 0.04$) (Table 1).

The median daily sedentary time at baseline was 609 min/day. Participants with a high sedentary time tended to be older, and had a higher BMI, but a lower diastolic BP compared to individuals with a low sedentary time. Besides, they were more likely to take kidney-protective and BP-lowering medication (all $p < 0.03$) (Table 1).

3.2. Cross-sectional analysis

There was an inverse association between baseline time spent in MVPA and the presence of albuminuria at baseline (OR: 0.82; 95 % CI: 0.69–0.98) in the fully adjusted logistic regression. In addition, the OR of albuminuria was 1.09 (95 % CI: 0.95–1.25) per 60 min/day increase in sedentary time measured at baseline. The risk estimates were comparable across all three models for both sedentary time and MVPA (Table 2).

3.3. Progression analysis

The odds of progressing from UACR <30 mg/g to ≥30 mg/g from baseline to 4-years follow-up were inversely associated with baseline MVPA (OR: 0.74; 95 % CI: 0.59–0.94) (Table 3), and the same inverse association was present when progression from 30–300 mg/g to ≥300 mg/g was included in the model (OR: 0.78; 95 % CI: 0.63–0.98) (ESM Table S1). When only including participants who did not change their use of kidney-protective medication during the follow-up period the numerical value was unchanged (OR: 0.76; 95 % CI: 0.56–1.03) (ESM Table S2). When investigating interactions, age interacted significantly with the association between MVPA and UACR (OR ≥ 65 years: 0.37; 95 % CI: 0.21–0.67 and OR < 65 years 0.99; 95 % CI: 0.78–1.26, $p_{interaction} < 0.01$), but no other confounder showed any sign of interaction (Fig. 1).

We found no significant association between sedentary time measured at baseline and development of albuminuria (OR: 1.00; 95 % CI: 0.84–1.20) (Table 3). Similar results were found in the sensitivity analyses (ESM Tables S1, S2).

The individuals with accelerometer measurements at both baseline and 4-years follow-up demonstrated a median change in MVPA of −1.6 min/day (IQI −7.0 min/day, 1.7 min/day). The median change in sedentary time was 10.5 min/day (IQI −42.2 min/day, 57.7 min/day) (data not shown).

In the change-analysis, the OR of progressing to albuminuria per 10 min/day increase in MVPA from baseline to 4-years follow-up were 0.79 (95 % CI: 0.42–1.49) after adjustment for known confounders. The OR of progressing to albuminuria per 60 min/day increase in sedentary time were 1.03 (95 % CI: 0.98–1.09) from baseline to 4-years follow-up (Table 4).

3.4. Sensitivity analyses

There was no difference in change in the use of kidney-protective medication from baseline to 4-years follow-up in the dichotomous groups of neither MVPA nor sedentary time (ESM Table S5).

Among the 881 participants in this study, 759 (93.4 %) had UACR measured at 4-years follow-up. Sensitivity analysis showed that participants with UACR measured at 4-years follow-up tended to spend longer time in MVPA and were more likely to take lipid-lowering medications at baseline (all $p < 0.02$). The groups were comparable across all other variables (ESM Table S3).

In another sensitivity analysis we compared baseline characteristics of the 459 individuals (52.1 %), who had their accelerometer measurements repeated at 4-years follow-up, to the ones who did not. The participants with accelerometer measurements at 4-years follow-up tended to spend longer time in MVPA and have a lower BMI. Additionally, they were less likely to smoke and more likely to take lipid-lowering medication at baseline (all $p < 0.02$) (ESM Table S4).

4. Discussion

Our study yielded three primary findings: 1) Longer time spent in MVPA at baseline was associated with lower presence of albuminuria at baseline as well as reduced progression to albuminuria after 4-years follow-up, 2) Time spent sedentary showed no significant associations with presence or incidence of albuminuria, and 3) Although associations between change in MVPA and development of albuminuria presented with wide confidence intervals, the direction as well as strength of the association was comparable with the odds of progression based on baseline MVPA, but the precision of the estimate was lower.

The inverse associations between baseline MVPA and both the presence and incidence of albuminuria after 4-years follow-up, show

Table 2
Cross-sectional odds of having albuminuria depending on moderate to vigorous physical activity (MVPA) and sedentary time (ST).

		Albuminuria								
	N	Model 1	*p*-Value	95 % CI	Model 2	*p*-Value	95 % CI	Model 3	*p*-Value	95 % CI
MVPA	832	0.82	0.01	0.70; 0.96	0.79	0.01	0.67; 0.94	0.82	0.03	0.69; 0.98
ST	832	1.11	0.11	0.98; 1.26	1.11	0.11	0.98; 1.27	1.09	0.20	0.95; 1.25

Note: Estimates derive from logistic regression analyses. The odds ratios represent 10 min/day increase in MVPA or 60 min/day in ST. Albuminuria is defined as UACR ≥ 30 mg/g.

Abbreviations: ACE, Angiotensin converting enzyme-inhibitors; ARA, Mineralocorticoid receptor antagonists; ARB, Angiotensin receptor blockers; BMI, Mody Mass Index; BP, Blood pressure; CI, Confidence interval; SGLT-2, Sodium-glucose cotransporter-2-inhibitors; UACR, Urine albumin/creatinine-ratio.

Model 1: Univariate odds ratio.

Model 2: Odds ratio adjusted for age and sex.

Model 3: Odds ratio adjusted for age, sex, smoking, BMI, LDL-cholesterol, diabetes duration, HbA1c, systolic BP, alcohol intake, cardiovascular disease, cancer and baseline use of kidney-protective medication (ACE, ARA, ARB, SGLT2 and GLP-1).

Table 3
Odds of progressing to albuminuria from baseline to 4-years follow-up depending on moderate to vigorous physical activity (MVPA) and sedentary time (ST) measured at baseline.

		Albuminuria								
	N	Model 1	*p*-Value	95 % CI	Model 2	*p*-Value	95 % CI	Model 3	*p*-Value	95 % CI
MVPA	659	0.79	0.02	0.66; 0.96	0.80	0.02	0.66; 0.97	0.74	0.01	0.59; 0.94
ST	659	1.10	0.24	0.94; 1.28	1.07	0.37	0.92; 1.26	1.00	0.97	0.84; 1.20

Note: Estimates derive from logistic regression analyses. The odds ratios represent 10 min/day increase in MVPA or 60 min/day in ST. Albuminuria is defined as UACR $\geq$ 30 mg/g.
Abbreviations: ACE, Angiotensin converting enzyme-inhibitors; ARA, Mineralocorticoid receptor antagonists; ARB, Angiotensin receptor blockers; BMI, Mody Mass Index; BP, Blood pressure; CI, Confidence interval; SGLT-2, Sodium-glucose cotransporter-2-inhibitors; UACR, Urine albumin/creatinine-ratio.
Model 1: Univariate odds ratio.
Model 2: Odds ratio adjusted for age and sex.
Model 3: Odds ratio adjusted for age, sex, smoking, BMI, LDL-cholesterol, diabetes duration, HbA1c, systolic BP, alcohol intake, cardiovascular disease, cancer, change in use of kidney-protective medication (ACE, ARA, ARB, SGLT2 and GLP-1) from baseline to 4-years follow-up and baseline UACR.

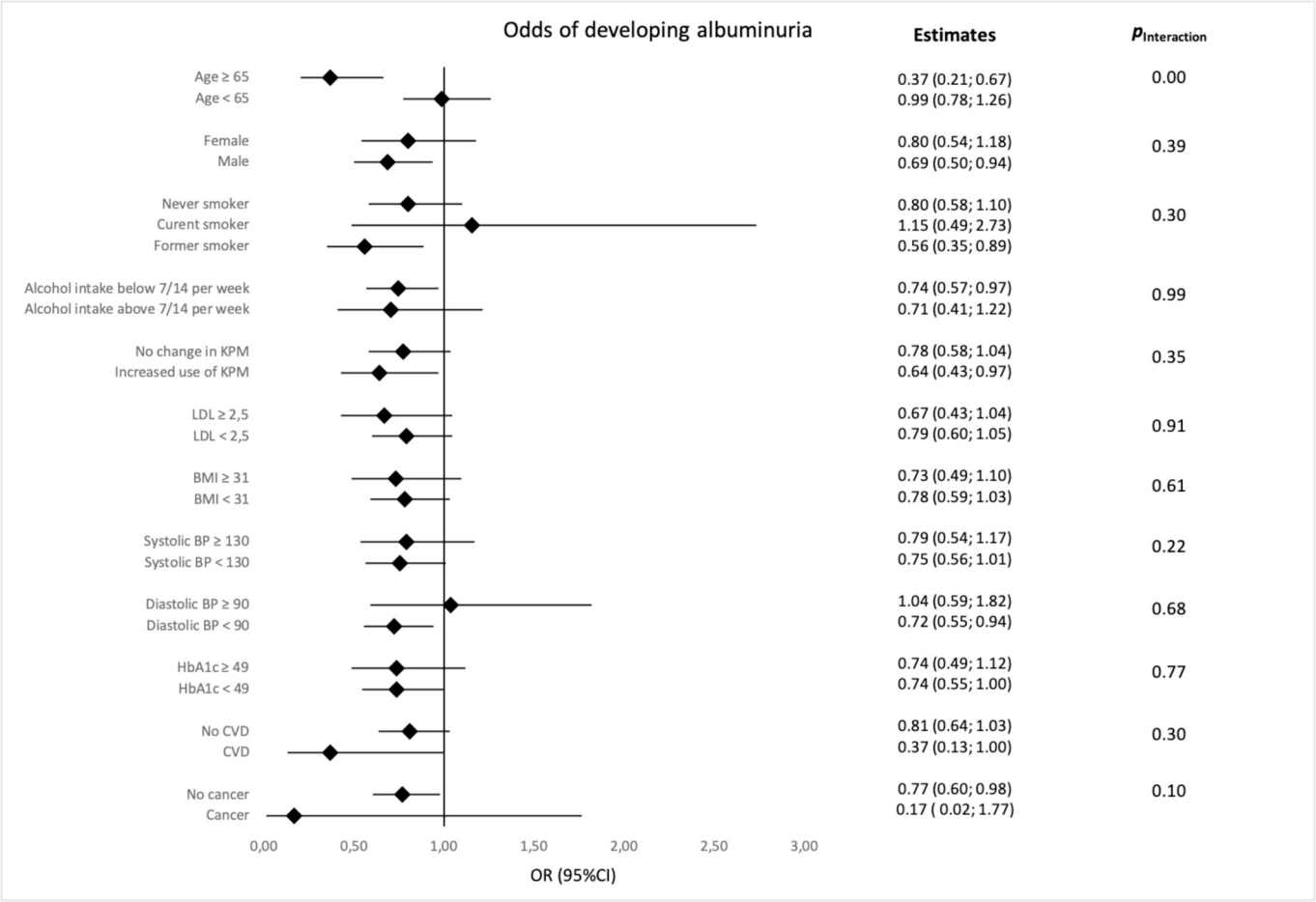

Fig. 1. Forest plot illustrating interactions between progression to albuminuria from baseline to 4-years follow-up and moderate to vigorous physical activity (MVPA) measured at baseline. Note: Estimates derive from logistic regression analyses. Albuminuria is defined as UACR $\geq$ 30 mg/g. Abbreviations: ACE, Angiotensin converting enzyme-inhibitors; ARA, Mineralocorticoid receptor antagonists; ARB, Angiotensin receptor blockers; BMI, Mody Mass Index; BP, Blood pressure; CI, Confidence interval; CVD, Cardiovascular disease; KPM, Kidney-protective Medication; LDL, Low-density lipoprotein; SGLT-2, Sodium-glucose cotransporter-2-inhibitors; UACR, Urine albumin/creatinine-ratio.
Odds ratio adjusted for age, sex, smoking, BMI, LDL-cholesterol, diabetes duration, HbA1c, systolic BP, alcohol intake, cardiovascular disease, cancer, change in use of kidney-protective medication (ACE, ARA, ARB, SGLT-2 and GLP-1) from baseline to 4-years follow-up and baseline UACR.

that physically active individuals with type 2 diabetes are less likely to develop albuminuria. Thus, our results extend previous findings in a longitudinal study in a populations-based sample[15] and in a systematic review containing 2.755.719 participants from various populations.[16] The same results have further been reported in studies of individuals with type 2 diabetes, although participants were not necessarily recently diagnosed and physical activity was self-reported.[17,18] Our study confirms these findings using accelerometer-measured physical activity in individuals with recently diagnosed type 2 diabetes. Besides, our interaction analysis showed a stronger association between MVPA and UACR for participants above 65 years.

The findings of our study also align with findings from a very recent

Table 4
Odds of progressing to albuminuria from baseline to 4-years follow-up depending on change in moderate to vigorous physical activity (MVPA) and sedentary time (ST) from baseline to 4-years follow-up.

		Albuminuria								
	N	Model 1	*p*-Value	95 % CI	Model 2	*p*-Value	95 % CI	Model 3	*p*-Value	95 % CI
ΔMVPA	337	1.09	0.57	0.81; 1.46	1.10	0.54	0.82; 1.47	0.79	0.47	0.42; 1.49
ΔST	336	0.99	0.72	0.95; 1.04	1.00	0.85	0.95; 1.04	1.03	0.26	0.98; 1.09

Note: Estimates derive from logistic regression analyses. The odds ratios represent 10 min/day increase in MVPA or 60 min/day increase in ST from baseline to 4-years follow-up. Albuminuria is defined as UACR $\geq$ 30 mg/g.
Abbreviations: ACE, Angiotensin converting enzyme-inhibitors; ARA, Mineralocorticoid receptor antagonists; ARB, Angiotensin receptor blockers; BMI, Mody Mass Index; BP, Blood pressure; CI, Confidence interval; LDL-c, Low-density lipoprotein-cholesterol; SGLT-2, Sodium-glucose cotransporter-2-inhibitors; UACR, Urine albumin/creatinine-ratio.
Model 1: Univariate odds ratio.
Model 2: Odds ratio adjusted for age and sex.
Model 3: Odds ratio adjusted for age, sex, smoking, BMI, LDL-cholesterol, diabetes duration, HbA1c, systolic BP, alcohol intake, cardiovascular disease, cancer, change in use of kidney-protective medication (ACE, ARA, ARB, SGLT-2 and GLP-1) from baseline to 4-years follow-up, baseline UACR and baseline MVPA/ST.

longitudinal study, performed in 1746 individuals with type 2 diabetes and overweight or obesity.[32] This study showed that increased MVPA was associated with a lower risk of progression to CKD, defined solely by a low eGFR, yet the study did not evaluate on the risk of developing albuminuria. Another longitudinal study in 326 individuals recently diagnosed with type 2 diabetes did not find an association between interventional change in MVPA from baseline to 4-years follow-up and the risk of developing albuminuria.[20] In our study, the association between the change in MVPA and the risk of developing albuminuria was inconclusive with a low statistical precision, partly due to the low number of study participants with repeated accelerometer measures at follow-up. Additionally, we only detected minimal changes in MVPA within our study population during the follow-up period (IQI -7.0 min/day, 1.7 min/day) and the fact that the change may only have occurred at the time of the follow-up and not in the intermediate period might also have affected the analysis. Likewise, a small-scale intervention study in 30 male participants with type 2 diabetes, who underwent regular interventional exercise for 6 months, showed a reduced UACR following the intervention period.[33] This combination of results suggests that spending more time in MVPA may lower the risk of progressing to albuminuria and CKD in individuals with type 2 diabetes. To evaluate the effect of increasing MVPA more precisely, larger sample sizes with larger changes from baseline to follow-up is needed. This will require a targeted and progressive physical activity intervention with high adherence.

In this study, we found no significant association between sedentary time and neither presence of albuminuria at baseline nor incidence of albuminuria after 4-years follow-up, although the positive direction of the association was clear and consistent throughout the analyses. Several cross-sectional studies using self-reported physical activity in individuals without type 2 diabetes have reported a positive association between sedentary time and albuminuria.[14,34] Additionally, a longitudinal study using accelerometer-measured sedentary time in individuals without type 2 diabetes found that prolonged sedentary time was associated with higher odds of CKD,[15] yet they did not evaluate on the risk of developing albuminuria. Another longitudinal study performed in individuals with type 2 diabetes showed a positive association between sedentary time and serum creatinine, but no association with neither eGFR nor albuminuria.[20] Overall, these studies, including ours, have shown inconclusive associations between sedentary time and albuminuria.

Our study findings indicate a stronger association between MVPA and albuminuria than between sedentary time and albuminuria. This indicates that it is important to not just refrain from being sedentary, but to engage in MVPA to achieve the biggest impact on kidney-related health factors. This might be explained by the fact that more time in MVPA entails a lesser risk of hypertension, obesity, hypercholesterolemia and inflammation,[6–10] which may all potentially lower the risk of albuminuria. Nonetheless, individuals with more time spent in MVPA might also be a selected group that generally lives healthier than the general population and therefore has a better renal prognosis.

4.1. Strengths

The accelerometer-based measurements of physical activity strengthen the study, since it provides an objective measure of physical activity volume and intensity, thereby minimizing the risk of information bias. Besides, with a cohort of individuals recently diagnosed with type 2 diabetes and a follow-up period of 4 years, this is one of the first studies to investigate the association between accelerometer-measured physical activity and albuminuria in type 2 diabetes prospectively. Furthermore, our results were robust to confounder adjustment and the risk of selection bias was minimal. Hence sensitivity analyses showed that the only differences observed between those who had UACR measured at 4-years follow-up (93 %) and those who did not (7 %) was that the attendees had a higher baseline MVPA and a larger use of lipid-lowering medication (ESM Table S3). Additionally, of the 832 participants with physical activity and UACR measured at baseline, only 34 participants died between baseline and 4-years follow, representing approximately 4.5 % of participants with high MVPA and 1 % of participants with low MVPA. Altogether, this indicates a low risk of selection bias due to loss to follow-up.

When we incorporated progression from microalbuminuria to macroalbuminuria, the consistent inverse association with time spent in MVPA persisted with negligible change in the odds ratios compared to the main results (ESM Table S1). Also, keeping use of kidney-protective medication constant, the odds ratios remained unchanged, albeit insignificant, likely due to the reduced sample size (ESM Table S2). This indicates a robust and clear inverse association between MVPA and albuminuria across various conditions.

4.2. Limitations

This study is limited by the small sample size with available accelerometer-measurements at follow-up compared to baseline. A post-hoc power calculation showed that 587 participants were needed to achieve 80 % power to detect a clinically meaningful effect (defined as 10 % change in the odds of developing albuminuria) in the change-analysis (data not shown) and this study only contained 337 participants.[35] Combined with the minimal changes in MVPA from baseline to follow-up in the study group, this may have hindered the detection of statistically significant associations between change in physical activity and progression to albuminuria. If the study had contained an intervention with regular and progressive MVPA, it is more likely that a possible association would be evident.

Furthermore, a selection bias due to loss to follow-up might have

been induced in the change-analysis, since only 52.1 % of participants with accelerometer-measurements at baseline had these repeated at 4-years follow-up. Hence sensitivity analysis showed that the participants who attended 4-years follow-up tended to be healthier than the ones who did not (ESM Table S4). Only investigating a healthier part of the population not only decreases generalizability, but it may also cause less variance and thereby decrease the chances of detecting statistically significant differences.

Additionally, since the analyzed data derive from a non-randomized intervention study, participants received varying pharmacological interventions during the study period depending on their baseline characteristics.[21]

4.3. Conclusion

This study showed an inverse association between accelerometer-measured MVPA at baseline and both the presence of albuminuria at baseline and the incidence of albuminuria after 4-years follow-up in individuals recently diagnosed with type 2 diabetes at baseline. An increase in MVPA from baseline to follow-up inferred 21 % lower incidence of albuminuria after 4-years follow-up, albeit insignificant, likely due to the relatively small sample size at follow-up and the lack of larger changes in physical activity. Likewise, we found no significant association between sedentary time and albuminuria. Thus, additional longitudinal studies with larger sample sizes at follow-up and randomized interventions entailing larger changes in measures of physical activity from baseline to follow-up are required to investigate the association between changes in physical activity and the risk of developing renal disease in type 2 diabetes.

CRediT authorship contribution statement

T. Norlén: Writing - Original Draft, Investigation, Formal analysis, Data curation, Conceptualization. **T.B. Olesen:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation, Conceptualization. **S.L. Domazet:** Writing – review & editing, Supervision, Investigation, Data curation, Conceptualization. **J.S. Nielsen:** Writing – review & editing, Supervision, Conceptualization. **J.C. Brønd:** Writing – review & editing, Project administration, Data curation. **M.H. Olsen:** Writing – review & editing, Supervision, Formal analysis, Conceptualization. **K. Højlund:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization. **J.V. Stidsen:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Funding

This study is based on data from the IDA study,[21] which was supported by the Danish Agency for Science (grant nos. 09-067009 and 09-075724), the Region of Southern Denmark, the Region of Zealand, the Augustinus Foundation, the Herta Christensen Foundation, the Novo Nordisk Foundation and the University of Southern Denmark. Project partners are listed on the project website (https://DD2.nu).

The funders were not involved in any aspects of this study, including: the design of the study, the collection, analysis, and interpretation of data, and writing the report. Nor did the funders impose any restrictions regarding the publication of this manuscript.

Declaration of competing interest

Michael Hecht Olsen has received payments or honoraria for lectures, presentations, or educational events from AstraZeneca, Novo Nordic A/S, and Teva A/S, and has an unpaid position as chair of the Danish Hypertension Society. The authors declare no conflict of interest associated with this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2025.109065.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request and approval by the Danish Data Protection Agency.

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