

SUPPLEMENTARY MATERIAL

Title: Physical activity and risk of microvascular complications in persons with type 2 diabetes: A UK Biobank study

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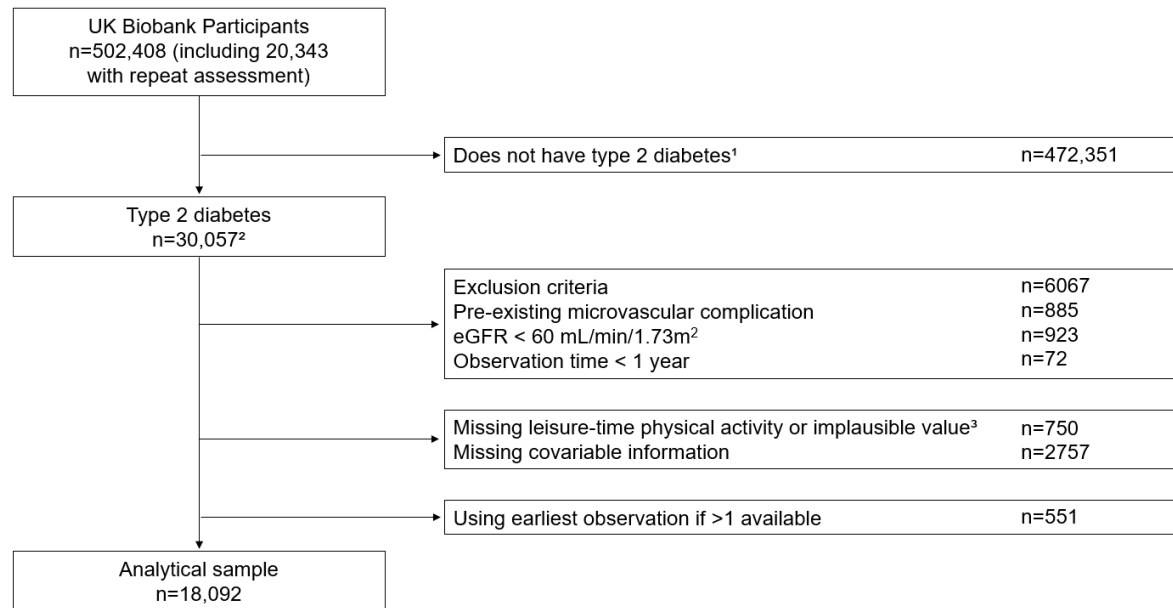
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Supplementary Table 1. Exclusion criteria based on medical history (interview data and hospital diagnosis codes), in addition to a history of any of the outcome codes

	Conditions	Data source
UK Biobank		
Metastatic cancer	ICD10: C76-C80	Cancer registry data (Field IDs: 40006, 40005)
HIV	ICD10: B21-B24 ICD9: 042	Verbal interview (Field ID: 20002) Hospital In-patient data (Field IDs: 41270, 41280, 41271, 41281)
Other subtypes of neuropathy (hereditary, inflammatory, alcohol- or drug induced, infectious, connective disorders, nutritional or neoplastic).	Hereditary motor and sensory neuropathy (G60), inflammatory polyneuropathy (G61), other polyneuropathies (G62, excluding G62.9), polyneuropathy in diseases classified elsewhere (G63, excluding G63.2), other disorders of peripheral nervous system (G64)	Hospital In-patient data (Field IDs: 41270, 41280)
Chronic immunological/systemic diseases	Rheumatoid arthritis, vasculitis, giant cell/temporal arteritis, polymyalgia rheumatica, Wegners granulomatosis, microscopic polyarteritis, polyarteritis nodosa, systemic lupus erythematosus, sjogren's syndrome/sicca syndrome, dermatopolymyositis, dermatomyositis, polymyositis, scleroderma/systemic sclerosis, chronic fatigue syndrome, antiphospholipid syndrome, amyloidosis	Verbal interview (Field ID: 20002) Amyloidosis: Hospital In-patient data (Field IDs: 41270, 41280 and ICD-10 diagnosis code: E85)
Liver failure/cirrhosis	Liver failure/cirrhosis, primary biliary cirrhosis, alcoholic liver disease / alcoholic cirrhosis	Verbal interview (Field ID: 20002)
Renal failure/reduced kidney function	Renal/kidney failure, renal failure requiring dialysis, renal failure not requiring dialysis, kidney nephropathy, IGA nephropathy, diabetic nephropathy, nephritis, glomerulonephritis, eGFR<60 ml/min/1.73 m ²	Verbal interview (Field ID: 20002) P-creatinine (Field ID: 30700)

Psychological/psychiatric problems	Schizophrenia, mania/bipolar disorder/manic depression, deliberate self-harm/suicide attempt, post-traumatic stress disorder	Verbal interview (Field ID: 20002)
Substance abuse/dependency	Alcohol dependency, opioid dependency, other substance abuse/dependency, chronic pancreatitis (ICD10: K860, K861)	Verbal interview (Field ID: 20002) Chronic pancreatitis: Hospital In-patient data (Field IDs: 41270, 41280)
Anorexia/bulimia/other eating disorder	Anorexia/bulimia/other eating disorder	Verbal interview (Field ID: 20002)
Chronic/degenerative neurological problem	Chronic/degenerative neurological problem, Parkinson's disease, dementia/Alzheimer's/cognitive impairment, motor neuron disease, myasthenia gravis, multiple sclerosis, other demyelinating disease (not multiple sclerosis)	Verbal interview (Field ID: 20002)
Unable to walk		Touch-screen questionnaire (Field ID: 864)
Living in care home		Touch-screen questionnaire (Field ID: 670)
Mobility allowance/receiving disability allowance/blue badge		Touch-screen questionnaire (Field ID: 6146)
Underweight	Body mass index < 18.5 kg/m ²	Height and weight measured by trained staff (Field ID: 21001)

Supplementary Figure 1. Participant flowchart



¹Prevalent type 2 diabetes defined by Eastwood algorithm and/or from measured HbA1c ≥ 48 mmol/mol.

²Observations, not unique participants.

³Sum of self-reported behaviors >24 hours/day.

Exact definitions of exclusion criteria are shown in Supplementary Table 1. Exclusion criteria included major somatic (e.g. metastatic cancer, kidney failure, or chronic immunological/systemic diseases, body mass index (BMI) < 18.5 kg/m²) or psychological (e.g. Parkinson's disease, schizophrenia, or substance abuse) conditions as well as those who were unable to walk, required attendance, disability, or mobility allowance, or lived in mobile or temporary structures, sheltered accommodation, or care homes.

Supplementary Table 2. Detailed definitions and operationalization of physical activity and covariables.

Data collection procedures	Self-administered questionnaire on a touch-screen, verbal interview, anthropometry, biochemistry, national registries
Physical activity	
Leisure-time physical activity	<p>Derived from questionnaire;</p> <p>Intensity: In the last 4 weeks did you spend any time doing the following; walking for pleasure/do strenuous sports/other exercises/light do-it-yourself/heavy do-it-yourself? <i>You can select more than one answer</i></p> <p>Frequency: How many times in the last 4 weeks did you go walking for pleasure/do strenuous sports/other exercises/light do-it-yourself/heavy do-it-yourself?</p> <p>Duration: Each time you went walking for pleasure/did strenuous sports/other exercises/light do-it-yourself/heavy do-it-yourself, about how long did you spend doing it?</p> <p>Above was combined to calculate MET-hrs/week based based on conventional metabolic equivalents of task (METs): walking (3.3), light do-it-yourself (2.25), heavy do-it-yourself (4.5), strenuous sport (8.0), and 'other exercise' (4.5) (1).</p>
Transportation physical activity	<p>Questionnaire;</p> <p>What types of transport do you use to get to and from work? (You can select more than one answer)</p> <ul style="list-style-type: none"> - Car/motor vehicle - Walk - Public transport - Cycle <p>Working from home was based on questions on distance and/or frequency of travels between home and work</p> <p>Included as passive, walking, cycling, or working from home</p>
Occupation physical activity	<p>Questionnaire;</p> <p>Does your work involve walking or standing for most of the time?</p> <p>Does your work involve heavy manual or physical work?</p> <ul style="list-style-type: none"> - Never/rarely - Sometimes - Usually - Always <p>Included as sedentary work, some standing and no heavy work, heavy manual work, not in employment, or retired</p>
Sociodemographic	
Age	Attendance date minus birthdate, day of birth set to the 15 th
Education	<p>Questionnaire;</p> <p>Which of the following qualifications do you have? (You can select more than one)?</p> <ul style="list-style-type: none"> - College or university degree - A levels/AS levels or equivalent - O levels/GCSEs or equivalent - CSEs or equivalent - NVQ or HND or HNC or equivalent - Other professional qualifications eg: nursing, teaching <p>Included as no qualifications, qualifications, not college/university degree, or college/university degree</p>
Deprivation	Townsend deprivation index calculated from post-codes
Living with partner	<p>Questionnaire;</p> <p>How are the other people who live with you related to you? (You can select more than one answer)</p> <ul style="list-style-type: none"> - Husband, wife or partner - Son and/or daughter (include step-children) - Brother and/or sister - Mother and/or father)

	<ul style="list-style-type: none"> - Grandparent - Grandchild - Other related - Other unrelated <p>Included as living with partner, yes/no</p>
Ethnicity	<p>Questionnaire; What is your ethnic group?</p> <ul style="list-style-type: none"> - White - Mixed - Asian or Asian British - Black or Black British - Chinese - Other ethnic group <p>Included as European, South Asian, African Caribbean, or other</p>
Behavioral	
Smoking	<p>Derived from questionnaire; Do you smoke tobacco now?</p> <ul style="list-style-type: none"> - Yes, on most or all days - Only occasionally - No <p>In the past, how often have you smoked tobacco?</p> <ul style="list-style-type: none"> - Smoked on most or all days - Smoked occasionally - Just tried once or twice - I have never smoked <p>Included as never, former or current</p>
Alcohol intake	<p>Derived from questionnaire; About how often do you drink alcohol?</p> <ul style="list-style-type: none"> - Daily or almost daily - Three or four times a week - Once or twice a week - One to three times a month - Special occasions only - Never <p>Did you previously drink alcohol?</p> <ul style="list-style-type: none"> - Yes - No <p>Included as never, former, current (<3 times/week), or current (≥3 times/week)</p>
Dietary quality	<p>Derived from questionnaire; How often do you eat processed meats (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets)? How often do you eat beef? (Do not count processed meats) How often do you eat lamb/mutton? (Do not count processed meats) How often do you eat pork? (Do not count processed meats such as bacon or ham) How often do you eat oily fish? (e.g. sardines, salmon, mackerel, herring) How often do you eat other types of fish? (e.g. cod, tinned tuna, haddock)</p> <ul style="list-style-type: none"> - Never - Less than once a week - Once a week - 2-4 times a week - 5-6 times a week - Once or more daily <p>On average how many heaped tablespoons of COOKED vegetables would you eat per DAY? (Do not include potatoes; put '0' if you do not eat any)</p>

	<p>On average how many heaped tablespoons of SALAD or RAW vegetables would you eat per DAY? (Include lettuce, tomato in sandwiches; put '0' if you do not eat any)</p> <p>About how many pieces of FRESH fruit would you eat per DAY? (Count one apple, one banana, 10 grapes etc as one piece; put '0' if you do not eat any)</p> <p>About how many pieces of DRIED fruit would you eat per DAY? (Count one prune, one dried apricot, 10 raisins as one piece; put '0' if you do not eat any)</p> <p>- <i>Free text answer</i></p> <p>Included as dietary quality index based on minimum 400 grams of fruit or vegetable/day, ≤ 3 servings of red meat + ≤ 1 serving of processed meat/week, and ≥ 2 servings of fish including 1 with oily fish/week. Meeting 0, 1 or 2-3 targets.</p>
Health-related	
BMI	Height and weight measured by trained staff; Calculated as weight (kg) / height (m) ²
Waist circumference	Measured by trained staff; Measured at the narrowest part of the torso
Depression	Verbal interview; Included as yes/no
Loneliness	Questionnaire; Do you often feel lonely? Included as yes/no
Family history of type 2 diabetes, CVD, or cancer	<p>Questionnaire;</p> <p>Has/did your father ever suffer from? (You can select more than one answer)</p> <p>Has/did your mother ever suffer from? (You can select more than one answer)</p> <p>Have any of your brothers or sisters suffered from any of the following diseases? (You can select more than one answer)</p> <p>Has/did your ADOPTED father ever suffer from? (You can select more than one answer)</p> <p>Has/did your ADOPTED mother ever suffer from? (You can select more than one answer)</p> <p>Have any of your ADOPTED brothers or sisters suffered from any of the following diseases? (You can select more than one answer)</p> <ul style="list-style-type: none"> - Prostate cancer - Severe depression - Parkinson's disease - Alzheimer's disease/dementia - Diabetes - High blood pressure - Chronic bronchitis/emphysema - Breast cancer - Bowel cancer - Lung cancer - Stroke - Heart disease <p>Included as family history of diabetes, cardiovascular disease, or cancer, yes/no</p>
History of cardiovascular disease	<p>Hospital registries;</p> <p>Myocardial infarction, stroke, ischaemic stroke, subarachnoid haemorrhage, brain haemorrhage (using codes listed in https://biobank.ndph.ox.ac.uk/showcase/refer.cgi?id=460) in addition to</p> <p>Angina: I20.0, I20.1, I20.8, I20.9 (all ICD-10) + 4139 (ICD-9)</p> <p>Heart failure: I11.0, I11.9, I13.0, I13.2, I13.9, I50.0, I50.1, I50.9 (all ICD-10) + 4280, 4281, 4289 (ICD-9)</p> <p>Included as yes/no</p>
History of cancer	<p>Derived from combination of questionnaire, verbal interview and cancer registry;</p> <p>"Has a doctor ever told you that you have had cancer?"</p> <p>Verbal interview excluding non-melanoma skin cancer (cancer codes: 1060, 1061, 1062, 1073)</p>

	Any cancer-type (C-D48) listed in the cancer registry, excluding metastatic + non-melanoma skin cancer Included as yes/no
Diabetes duration	Calculated as attendance date minus age at diabetes diagnosis
Type 2 diabetes inclusion method	<p>Derived from questionnaire and verbal interview; Has a doctor ever told you that you have diabetes?</p> <ul style="list-style-type: none"> - Yes - No <p>Did you only have diabetes during pregnancy?</p> <ul style="list-style-type: none"> - Yes - No - Not applicable <p>What was your age when the diabetes was first diagnosed?</p> <ul style="list-style-type: none"> - <i>Free text answer</i> <p>Did you start insulin within one year of your diagnosis of diabetes?</p> <ul style="list-style-type: none"> - <i>Free text answer</i> <p>Do you regularly take any of the following medications? (You can select more than one answer)</p> <ul style="list-style-type: none"> - Cholesterol lowering medication - Blood pressure medication - Insulin - Hormone replacement therapy - Oral contraceptive pill or mini pill - None of the above <p>What is your ethnic group?</p> <ul style="list-style-type: none"> - White - Mixed - Asian or Asian British - Black or Black British - Chinese - Other ethnic group <p>Combined with measured HbA1c and included as inclusion from self-reported type 2 diabetes/use of diabetes medication or from biochemistry</p>
Use of medication	<p>Derived from verbal interview; Type and number of prescription medications taken. See Supplementary Table 2 for definitions based on UK Biobank medication codes.</p> <p>Included as; use of statins, yes/no use of blood-pressure lowering drugs, 0, 1, 2, ≥ 3 Use of glucose-lowering drugs, none, insulin only, oral only, or oral + insulin</p>
Estimated glomerular filtration rate	<p>Derived from biochemistry; Calculated from serum creatinine according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations (2).</p>
HbA1c	<p>Biochemistry; Measured by HPLC analysis on a Bio-Rad VARIANT II Turbo</p>
LDL-cholesterol	<p>Biochemistry; LDL-direct measured by enzymatic protective selection analysis on a Beckman Coulter AU5800</p>
Systolic blood pressure	<p>Measured by trained staff; Mean of two measurements by Omron device. A manual sphygmometer was used if the standard automated device could not be employed.</p>

Supplementary Table 3. ICD-10 codes used to determine microvascular complications.

Neuropathy	E104, E114, E124, E134, E144 G590 G629 G632 G990
Nephropathy	E102, E112, E122, E132, E142 I120 I130, I131, I132, I139 N180, N181, N182, N183, N184, N185, N188, N189 N19 Z992
Retinopathy	E103, E113, E123, E133, E143 H330, H332, H333, H334, H335 H350, H353, H356, H357, H358, H359 H360 H430, H431, H438 H540, H541 I708

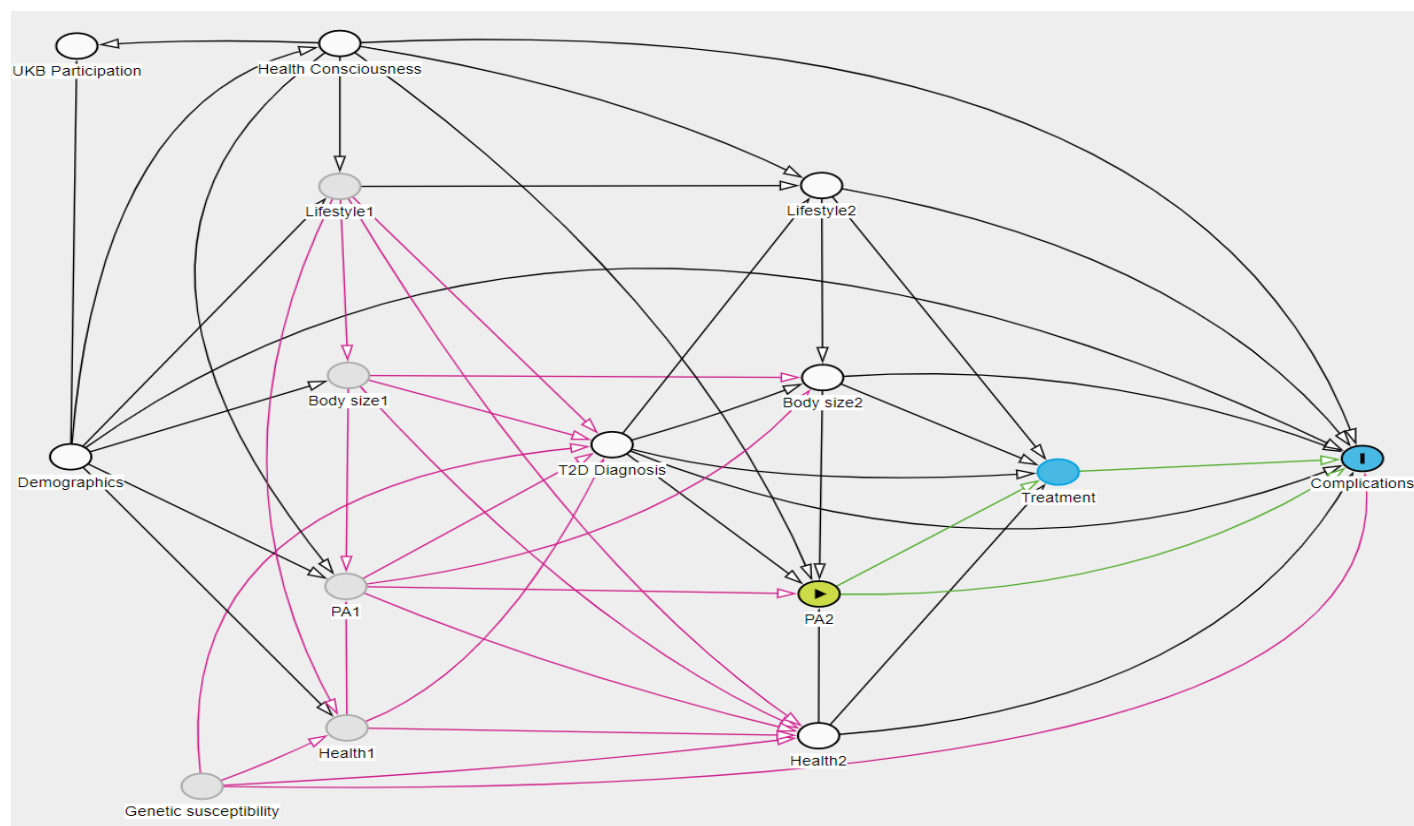
Supplementary Table 4. UK Biobank medication codes

Drug types	Sub-category	Codes
Lipid-lowering		
	Statins	1141146234, 1140888594, 1140888648, 1141192410, 1140861958, 1141146138, 1140864592, 1140861970, 1141192414, 1141200040, 1140881748
Blood pressure-lowering		
	Beta-blockers	1140916342, 1140866724, 1140866738, 1140860192, 1140860292, 1140860404, 1140860308, 1140860312, 1141194804, 1140860316, 1140860320, 1140860322, 1140860332, 1140860336, 1140860340, 1141194808, 1140860342, 1140860418, 1140860422, 1140860426, 1140864950, 1140909368, 1141164276, 1141162898, 1141169516, 1141184722, 1140879758, 1140879760, 1140879762, 1140879818, 1140879822, 1140879824, 1140879830, 1140879834, 1140879842, 1140879854, 1140879866, 1141180778, 1141146124, 1141146126, 1141194810, 1141146128, 1140866692, 1140916342, 1140866704, 1140866764, 1140866766, 1140851556, 1140866778, 1140866782, 1140866784, 1140866798, 1140866802, 1140866800, 1140866804, 1140916730, 1140916868, 1140917076, 1141152076, 1140866712, 1141156754, 1141156808, 1141172742, 1140866726, 1140866756, 1140860172, 1140864410, 1140922930, 1140860232, 1140860244, 1140860250, 1140860266, 1140860274, 1140860278, 1140860180, 1140860194, 1140860212, 1140851576, 1140851480, 1140860220, 1140860222, 1140851484, 1140860230, 1140910614, 1140860294, 1140851492, 1140860304, 1140860362, 1140860380, 1140860382, 1140860386, 1140860390, 1140860394, 1140860396, 1140860398, 1140860400, 1140860402, 1140860406, 1140860314, 1140860318, 1140851508, 1140860324, 1140860328, 1140860330, 1140860334, 1140860338, 1140916628, 1140860348, 1141146184, 1140860352, 1140860356, 1140860358, 1140860434, 1140860492, 1141171152, 1141184324, 1141182904, 1140866724, 1140866738, 1140860192, 1140860292, 1140860404, 1140860308, 1140860312, 1141194804, 1140860316, 1140860320, 1140860322, 1140860332, 1140860336, 1140860340, 1141194808, 1140860342, 1140860418, 1140860422, 1140860426, 1140864950, 1140909368, 1141164276, 1141162898, 1141169516, 1141184722, 1140879758, 1140879760, 1140879762, 1140879818, 1140879822, 1140879824, 1140879830, 1140879834, 1140879842, 1140879854, 1140879866, 1141180778, 1141146124, 1141146126, 1141194810, 1141146128, 1140866692, 1140916342, 1140866704, 1140866764, 1140866766, 1140851556, 1140866778, 1140866782, 1140866784, 1140866798, 1140866802, 1140866800, 1140866804, 1140916730, 1140916868, 1140917076, 1141152076, 1140866712, 1141156754, 1141156808, 1141172742, 1140866726, 1140866756, 1140860172, 1140864410, 1140922930, 1140860232, 1140860244, 1140860250, 1140860266, 1140860274, 1140860278, 1140860180, 1140860194, 1140860212, 1140851576, 1140851480, 1140860220, 1140860222, 1140851484, 1140860230, 1140910614, 1140860294, 1140851492, 1140860304, 1140860362, 1140860380, 1140860382, 1140860386, 1140860390, 1140860394, 1140860396, 1140860398, 1140860400, 1140860402, 1140860406, 1140860410, 1140860314, 1140860318, 1140851508, 1140860324, 1140860328, 1140860330, 1140860334, 1140860338, 1140916628, 1140860348, 1141146184, 1140860352, 1140860356, 1140860358, 1140860434, 1140860492, 1141171152, 1141184324, 1141182904

	Calcium channel blockers	1141165470, 1141150926, 1141153328, 1140926778, 1140851784, 1140861088, 1140861114, 1140911088, 1141150538, 1141157140, 1141169730, 1140861190, 1140879802, 1140888646, 1140861276, 1140928226, 1141153394, 1140872568, 1140879806, 1140879810, 1140888510, 1141153026, 1140861128, 1140851730, 1140861130, 1140861136, 1140861138, 1140861166, 1140926780, 1141157136, 1140911698, 1141151474, 1140917428, 1140917452, 1141153454, 1140923618, 1140861176, 1140861090, 1140923572, 1140851794, 1140926188, 1140926966, 1140861110, 1140927934, 1140927940, 1140861120, 1141145870, 1141150500, 1140916930, 1141152600, 1141166752, 1141162546, 1140851798, 1140851800, 1140861194, 1140861202, 1141200400, 1140928212, 1141187094, 1141188152, 1141188576, 1141188836, 1141188920, 1141190160, 1141199858, 1141200782, 1141201814, 1140861282, 1140928234, 1141153032, 1141153400, 1141167832, 1141175224, 1141171804, 1141174684, 1141180238, 1141173766, 1141187962, 1141188936, 1141190548
	Renin-angiotensin-system antagonists	1140860790, 1140888552, 1140864952, 1140860696, 1140860714, 1140888560, 1141180592, 1140860806, 1141165470, 1140860750, 1140860764, 1140888556, 1140923712, 1140860728, 1140860738, 1140860904, 1141153328, 1140860752, 1140860882, 1140866340, 1140860776, 1141170870, 1140881712, 1140860784, 1140860758, 1141150328, 1141167758, 1141150560, 1141151382, 1140860878, 1140860892, 1141164148, 1141164154, 1140881706, 1140860802, 1140860736, 1141188408, 1141199940, 1141200698, 1140860904, 1141153328, 1140860912, 1140860918, 1140923718, 1140860714, 1140860706, 1140864910, 1141153316, 1141145660, 1141201038, 1141145668, 1141201040, 1141156836, 1141156846, 1141171336, 1141171344, 1141172682, 1141152998, 1141153006, 1141172686, 1140916356, 1141151016, 1140916362, 1141151018, 1141179974, 1141193282, 1141193346, 1141166006, 1141187788, 1141187790, 1141172492, 1141187790, 1141172492
	Thiazides	1140866354, 1141187790, 1141151018, 1141172686, 1141201040, 1140851430, 1140851432, 1140866360, 1140866324, 1140866328, 1140860784, 1140860736, 1140866162, 1140860332, 1140926778, 1141151016, 1140860404, 1140860422, 1140860386, 1140860562, 1140860738, 1140860764, 1140860790, 1140864950, 1140864952, 1141172682, 1141187788, 1141201038, 1140851362, 1140851660, 1140866164, 1140866168, 1140864176, 1141194794, 1141194800, 1140866440, 1140851332, 1141194804, 1141194808, 1141194810, 1140866136, 1140866138, 1140860348, 1140866446, 1140866128, 1140866122, 1140860312, 1140860316, 1140860318, 1140860340, 1140860342, 1140860418, 1140866450, 1140910442, 1141146126, 1140866132, 1140866440, 1140851332, 1140888918, 1140866136, 1140866446, 1140851336, 1140866090, 1140851338, 1140909706, 1141180772, 1141180778, 1140860308, 1140923336, 1140864202, 1140866144, 1140851364, 1140866330, 1140866410, 1141146124, 1140923276, 1141146128, 1140851436, 1140860336, 1140866420, 1140866416, 1140866156, 1140866352, 1140851368, 1140866158, 1140866422, 1140923282, 1140866396, 1140866402, 1140866078, 1141180592, 1140888922, 1141146378, 1140917068, 1140866108, 1140866110, 1140866092, 1140866094, 1140866096, 1140866102, 1140866104, 1140860334, 1140860322, 1140860338, 1140866104, 1140860334, 1140860322, 1140860338
	Potassium-sparing diuretics	1140866334, 1140866332, 1140866418, 1140866412, 1140866406, 1141167108, 1140866396, 1140923282, 1140866422, 1140866352, 1140866416, 1140866420, 1140851436, 1141146128, 1140923276, 1140866410, 1140866330, 1141180772, 1140866402, 1141195254, 1140866408, 1140888512, 1140866354, 1140866426, 1140851430, 1140851432, 1140927174, 1140866222, 1140866226, 1140866220, 1140927174, 1140866360, 1140866388, 1140866324, 1140866328, 1140866390, 1140866236, 1140866244, 1140851418, 1140851420,

		1140851508, 1140866308, 1140866312, 1140866318, 1140866306, 1141201244, 1141201250, 1140866306, 1141201244, 1141201250
	Loop diuretics	1140866426, 1140866280, 1140866448, 1141168964, 1140866282, 1140866438, 1140866356, 1140909708, 1141195254, 1141195258, 1140851342, 1140851400, 1140851412, 1140866182, 1140866192, 1140866194, 1141167108, 1140851414, 1140866406, 1140866408, 1140866412, 1140866418, 1140851412, 1141169088, 1140866116, 1140860320, 1140866332, 1140866334, 1141169088, 1140866248, 1140866262, 1140888496, 1140864874, 1140866200, 1140866202, 1140866206, 1141157184, 1140866210, 1140866212, 1140866084, 1140866086, 1140866210, 1140866212, 1140866084, 1140866086
Glucose-lowering		
	Insulin	1140883066
	Metformin	1140884600, 1140874686, 1141189090
	Other	1141153254, 1141171646, 1141177600, 1140857584, 1140874706, 1140874664, 1140874674, 1140857494, 1140874744, 1140874646, 1141157284, 1140874658, 1141152590, 1141168660, 1141173882, 1141156984, 1140874724, 1140874726, 1140874746, 1140874650, 1140874652, 1141168660, 1141173882, 1141173786, 1140868902, 1140868908, 1141177606, 1141171652

Supplementary Figure 2. A Directed Acyclic Graph (DAG) of the association between physical activity and microvascular complications



Variables ending with 1: before type 2 diabetes

Variables ending with 2: after type 2 diabetes

Please see explanation on page 14.

The directed acyclic graph (DAG) was developed based on the template provided by Yang et al. (3). The DAG illustrates how lifestyle factors impacts the risk of developing type 2 diabetes as well as how lifestyle factors track over time (physical activity before type 2 diabetes predicts physical activity with type 2 diabetes). We have not included physical activity from other domains than leisure time in the DAG but will adjust for occupational and transportation physical activity.

Arrows from pre-diagnosis nodes to microvascular outcomes are omitted for simplicity.

As illustrated in the DAG, physical activity and health is connected through a reciprocal relationship where previous physical activity may affect current health, but current health may also impede current physical activity (PA1 -----> Health2 -----> PA2). Based on the data in UK Biobank, it is not possible to model this time-dependent relationship as we only observe participants when they already have diabetes. We thus consider Health2 as a strong confounding pathway.

Therefore, analysis will be based on the following logic;

- Remove from the analysis those individuals with a high risk of undiagnosed complications, potentially leading to reverse causation bias
- Multivariable-adjustment for duration of type 2 diabetes because complications tend to increase with time. We consider this an appropriate adjustment for poor health as physical activity does not affect duration of diabetes, but duration of diabetes may impact physical activity levels.
- No adjustment for use of glucose-, blood pressure-, or cholesterol lowering drugs (or their measured biomarker levels they are supposed to lower) in main model because physical activity may affect use of these drugs. They are therefore potential mediators of the effects of physical activity on microvascular diabetes complications.
- Under this DAG, there may be confounding from health consciousness. To address this, we have included an indicator for family history of major non-communicable diseases as a marker of health consciousness (may also be a marker of genetic susceptibility to those conditions).
- Remove from the analysis those individuals with comorbidities/physical limitations with a high risk of limitations to be physically active, i.e., those participants would not be eligible for a trial testing the effect of physical activity on microvascular complications (see above for a list of exclusion criteria).

Supplementary Table 5. Expanded descriptive characteristics at study enrolment by level of physical activity

	No leisure-time physical activity	Below recommendations (>0-7.49 MET-hrs/week)	At recommendations (7.5-14.9 MET-hrs/week)	Above recommendations (≥15 MET-hrs/week)
N (% Women)	1756 (46.6)	6942 (41.1)	3586 (37.7)	5808 (29.5)
Age (years), mean (SD)	58.7 (7.1)	59.5 (7.2)	60.2 (7.0)	60.7 (6.9)
Duration of diabetes (years), mean (SD)	5.4 (7.1)	5.2 (6.6)	5.1 (6.8)	5.5 (7.2)
Body composition				
BMI (kg/m ²), mean (SD)	33.4 (6.5)	31.6 (5.7)	30.7 (5.2)	30.0 (4.9)
Waist circumference (cm), mean (SD)	106.7 (14.9)	103.1 (13.7)	101.2 (13.3)	99.8 (13.0)
Body mass index categories (kg/m ²), No. (%)				
18.5-25	123 (7.0)	685 (9.9)	431 (12.0)	793 (13.7)
25-30	452 (25.7)	2327 (33.5)	1328 (37.0)	2422 (41.7)
30-35	563 (32.1)	2264 (32.6)	1153 (32.2)	1781 (30.7)
≥35	618 (35.2)	1666 (24.0)	674 (18.8)	812 (14.0)
Biomarkers, mean (SD)				
HbA1c (mmol/mol)*	55.5 (14.5)	54.5 (14.4)	52.8 (13.4)	52.6 (13.6)
LDL-cholesterol (mmol/L)*	2.9 (0.8)	2.8 (0.9)	2.8 (0.8)	2.8 (0.8)
Triglyceride (mmol/L)***	2.2 (1.3)	2.2 (1.3)	2.2 (1.3)	2.1 (1.2)
Systolic blood pressure (mmHg)*	141.9 (17.6)	141.8 (17.4)	142.1 (17.0)	143.0 (17.3)
eGFR (mL/min/1.73m ²)*	93.0 (13.3)	91.7 (12.6)	91.4 (12.1)	90.3 (12.1)
Socioeconomic indicators				
Townsend Index, mean (SD)	0.5 (3.6)	-0.7 (3.3)	-1.1 (3.1)	-1.4 (3.0)
Living with partner (yes), No. (%)	1063 (60.5)	4793 (69.0)	2585 (72.1)	4346 (74.8)
Education, No. (%)				
No qualifications	520 (29.6)	1576 (22.7)	701 (19.5)	1158 (19.9)
Other qualifications than college/university degree	864 (49.2)	3595 (51.8)	1784 (49.7)	2931 (50.5)
College/University degree	372 (21.2)	1771 (25.5)	1101 (30.7)	1719 (29.6)
Ethnicity, No. (%)				
European	1448 (82.5)	6060 (87.3)	3233 (90.2)	5368 (92.4)
South Asian	115 (6.5)	364 (5.2)	158 (4.4)	180 (3.1)
African Caribbean	98 (5.6)	247 (3.6)	87 (2.4)	109 (1.9)
Other	95 (5.4)	271 (3.9)	108 (3.0)	151 (2.6)
Physical activity				
LTPA (MET-hours/wk), mean (SD)	0.0 (0.0)	3.2 (2.1)	10.8 (2.1)	36.6 (26.2)
Participation in sports, No. (%)	0 (0.0)	40 (0.6)	111 (3.1)	670 (11.5)

Occupational physical activity, No. (%)				
Sedentary	325 (18.5)	1210 (17.4)	550 (15.3)	654 (11.3)
Some standing, No heavy	246 (14.0)	1202 (17.3)	565 (15.8)	731 (12.6)
Heavy manual work	419 (23.9)	1342 (19.3)	595 (16.6)	926 (15.9)
Not in employment	223 (12.7)	568 (8.2)	251 (7.0)	391 (6.7)
Retired	543 (30.9)	2620 (37.7)	1625 (45.3)	3106 (53.5)
Transportation, No. (%)				
Passive	760 (43.3)	2965 (42.7)	1298 (36.2)	1677 (28.9)
Walking	133 (7.6)	416 (6.0)	193 (5.4)	238 (4.1)
Cycling	10 (0.6)	78 (1.1)	59 (1.6)	140 (2.4)
Working from home	87 (5.0)	295 (4.2)	160 (4.5)	256 (4.4)
Not in employment/retired	766 (43.6)	3188 (45.9)	1876 (52.3)	3497 (60.2)
Health behaviors, No. (%)				
Smoking				
Never	782 (44.5)	3309 (47.7)	1722 (48.0)	2598 (44.7)
Former	695 (39.6)	2882 (41.5)	1548 (43.2)	2716 (46.8)
Current	279 (15.9)	751 (10.8)	316 (8.8)	494 (8.5)
Alcohol intake				
Never	194 (11.0)	543 (7.8)	207 (5.8)	303 (5.2)
Former	145 (8.3)	345 (5.0)	177 (4.9)	265 (4.6)
Current, <3 times/week	1014 (57.7)	3884 (55.9)	1900 (53.0)	2871 (49.4)
Current, ≥3 times/week	403 (22.9)	2170 (31.3)	1302 (36.3)	2369 (40.8)
Diet quality index				
0 (lowest diet quality)	498 (28.4)	1507 (21.7)	678 (18.9)	1023 (17.6)
1	759 (43.2)	2873 (41.4)	1412 (39.4)	2122 (36.5)
2-3 (highest diet quality)	499 (28.4)	2562 (36.9)	1496 (41.7)	2663 (45.9)
Medical history, No (%)				
Family history of CVD, cancer or diabetes	1512 (86.1)	5922 (85.3)	3096 (86.3)	4963 (85.5)
Pre-existing CVD	247 (14.1)	778 (11.2)	414 (11.5)	691 (11.9)
Pre-existing cancer	171 (9.7)	630 (9.1)	324 (9.0)	552 (9.5)
Depression	141 (8.0)	398 (5.7)	161 (4.5)	254 (4.4)
Loneliness	532 (30.3)	1506 (21.7)	653 (18.2)	979 (16.9)
Identification of individuals with type 2 diabetes, No. (%)†				
Doctor diagnosis or on treatment for type 2 diabetes	1417 (80.7)	5585 (80.5)	2944 (82.1)	4818 (83.0)
Drug use, No. (%)				

**Use of blood-glucose lowering
drugs, No (%)‡**

None	381 (26.9)	1540 (27.6)	983 (33.4)	1637 (34.0)
Non-insulin only	858 (60.6)	3366 (60.3)	1655 (56.2)	2612 (54.2)
Insulin and non-insulin	126 (8.9)	458 (8.2)	180 (6.1)	316 (6.6)
Insulin monotherapy	52 (3.7)	221 (4.0)	126 (4.3)	253 (5.3)
Beta-blockers	329 (18.7)	1194 (17.2)	572 (16.0)	929 (16.0)
Calcium-channel blockers	422 (24.0)	1435 (20.7)	700 (19.5)	1180 (20.3)
Renin-angiotensin-system antagonists	904 (51.5)	3472 (50.0)	1779 (49.6)	2804 (48.3)
Thiazides	335 (19.1)	1137 (16.4)	632 (17.6)	870 (15.0)
Potassium-sparing diuretics	14 (0.8)	56 (0.8)	19 (0.5)	39 (0.7)
Loop diuretics	81 (4.6)	198 (2.9)	75 (2.1)	122 (2.1)
Statins	1153 (65.7)	4542 (65.4)	2406 (67.1)	3826 (65.9)

*HbA1c, n=17,065, eGFR, n=16,975, Systolic blood pressure, n=18,068, LDL-cholesterol, n=16,930, Triglyceride, n=16,954

†Individuals with type 2 diabetes identified from self-reported type 2 diabetes or use of glucose-lowering drugs. Remaining individuals identified from measured HbA1c.

‡Reported at nurse interview, individuals identified with type 2 diabetes solely from measured HbA1c are not included in the denominator.

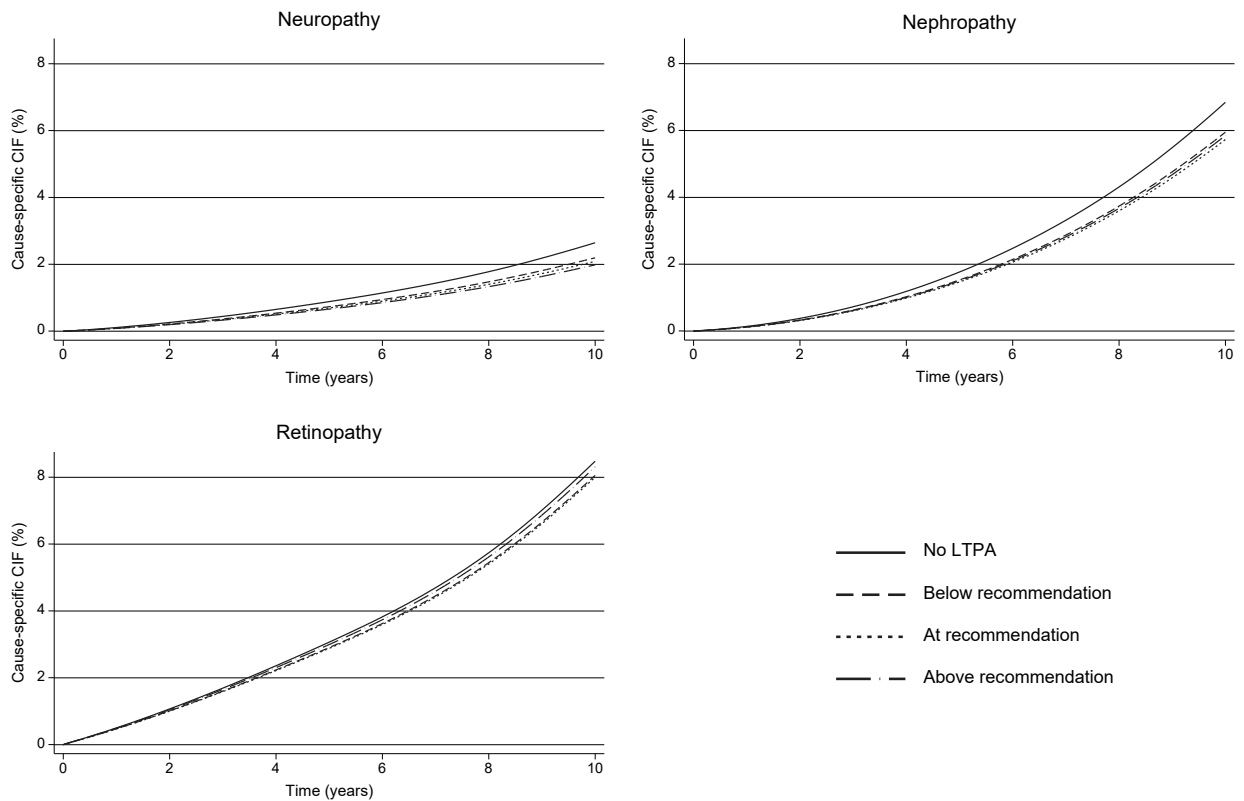
LTPA: leisure-time physical activity, CVD: cardiovascular disease

Supplementary Table 6. Adjusted (standardized) 10-year cumulative incidence (%) of microvascular complications

	No leisure-time physical activity	Below recommendations (>0-7.49 MET-hrs/week)	At recommendations (7.5-14.9 MET-hrs/week)	Above recommendations (≥15 MET-hrs/week)
Neuropathy				
Adjusted 10-year cumulative incidence (%)	2.78 (2.56, 3.03)	2.31 (1.97, 2.71)	2.19 (1.75, 2.74)	2.08 (1.72, 2.51)
Adjusted difference in 10-year cumulative incidence	reference	-0.47 (-0.79, -0.16)	-0.60 (-1.05, -0.14)	-0.71 (-1.06, -0.35)
<i>Death as competing event (2067 censoring events)</i>				
Adjusted 10-year cumulative incidence (%)	2.65 (2.33, 2.89)	2.20 (1.87, 2.58)	2.09 (1.67, 2.61)	1.98 (1.64, 2.40)
Adjusted difference in 10-year cumulative incidence	reference	-0.45 (-0.75, -0.15)	-0.56 (-1.00, -0.13)	-0.70 (-1.01, -0.33)
Nephropathy				
Adjusted 10-year cumulative incidence (%)	7.23 (6.87, 7.61)	6.29 (5.69, 6.95)	6.05 (5.23, 6.94)	6.16 (5.50, 6.90)
Adjusted difference in 10-year cumulative incidence	reference	-0.94 (-1.48, -0.40)	-1.18 (-1.96, -0.40)	-1.07 (-1.69, -0.44)
<i>Death as competing event (1733 censoring events)</i>				
Adjusted 10-year cumulative incidence (%)	6.85 (6.50, 7.21)	5.95 (5.38, 6.58)	5.73 (4.99, 6.58)	5.85 (5.22, 6.55)
Adjusted difference in 10-year cumulative incidence	reference	-0.90 (-1.41, -0.38)	-1.12 (-1.86, -0.38)	-1.00 (-1.59, -0.41)
Retinopathy				
Adjusted 10-year cumulative incidence (%)	8.86 (8.46, 9.28)	8.41 (7.62, 9.28)	8.33 (7.29, 9.52)	8.64 (7.75, 9.64)
Adjusted difference in 10-year cumulative incidence	reference	-0.45 (-1.18, 0.28)	-0.53 (-1.58, 0.52)	-0.22 (-1.07, 0.64)
<i>Death as competing event (1910 censoring events)</i>				
Adjusted 10-year cumulative incidence (%)	8.48 (8.10, 8.88)	8.06 (7.30, 8.89)	8.00 (7.00, 9.15)	8.31 (7.45, 9.27)
Adjusted difference in 10-year cumulative incidence	reference	-0.43 (-1.13, 0.28)	-0.48 (-1.49, 0.53)	-0.17 (-1.00, 0.65)

Based on model 3. Estimates were obtained from a flexible parametric survival model using restricted cubic spline functions with three knots (25th, 50th and 75th of the uncensored log survival times) to model the baseline cumulative hazard.

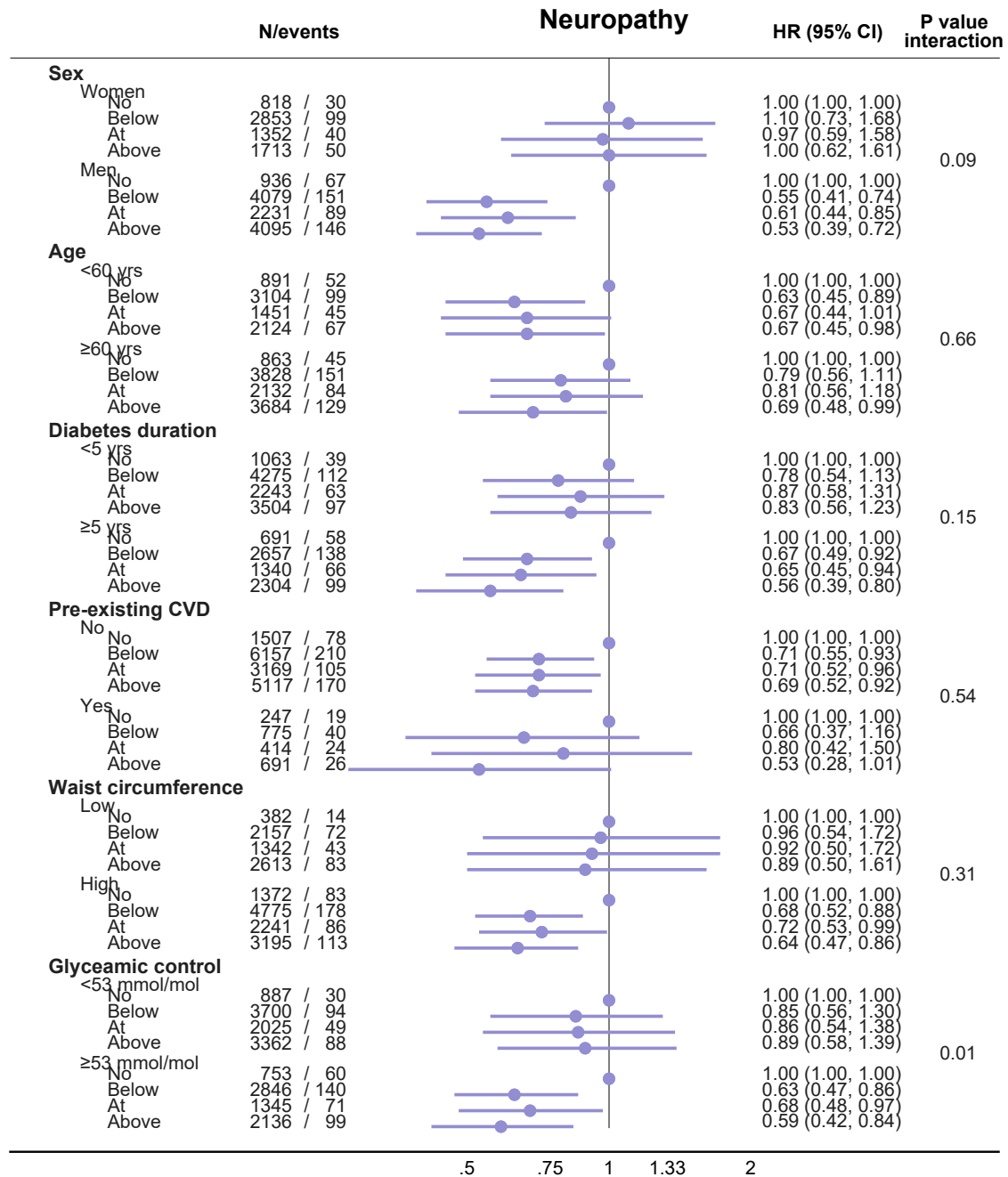
Supplementary Figure 3. Adjusted (standardized) 10-year cumulative incidence functions



Categories of leisure-time physical activity defined as; none (0 MET-hrs/week), below recommendation (>0 to 7.49 MET-hrs/week), at recommendation (7.5-14.9 MET-hrs/week), and above recommendation (≥ 15 MET-hrs/week). Estimates were obtained from a flexible parametric survival model using restricted cubic spline functions with three knots (25th, 50th and 75th of the uncensored log survival times) to model the baseline cumulative hazard.

The risk curves were adjusted for model 3 including sex, age (timescale), education (no qualifications, qualifications - not college/university degree, college/university degree), Townsend deprivation index (continuous), living with partner (yes/no), ethnicity (European, South Asian, African Caribbean, other), employment (sedentary work, some standing and no heavy work, heavy manual work, not in employment, retired), transportation (passive, walking, cycling, working from home), smoking (never, former, current), alcohol intake (never, former, current- <3 times/week, current- ≥ 3 times/week), diet quality index (0, 1, 2-3), family history of diabetes, CVD, or cancer (yes/no), diabetes status was self-reported (yes/no), depression (yes/no), loneliness (yes/no), pre-existing CVD, pre-existing cancer, and diabetes duration (continuous), and body mass index (continuous).

Supplementary Figure 4. Leisure-time physical activity and neuropathy stratified by participant characteristics

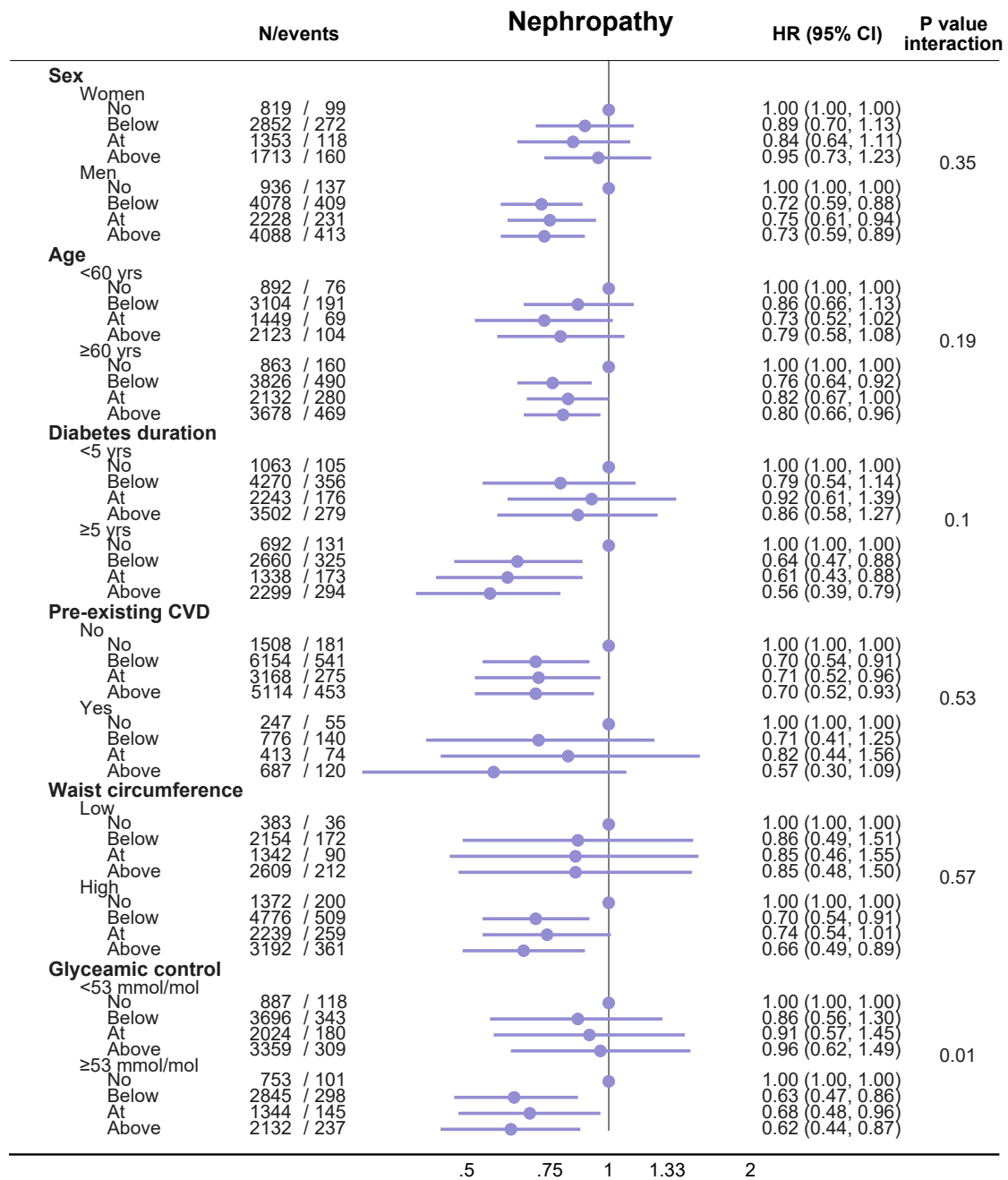


Categories of leisure-time physical activity defined as; none (0 MET-hrs/week), below recommendation (>0 to 7.49 MET-hrs/week), at recommendation (7.5-14.9 MET-hrs/week), and above recommendation (≥15 MET-hrs/week). Low waist circumference defined as <88/102 cm for women/men

Estimates were adjusted for model 3 including sex, age (timescale), education (no qualifications, qualifications - not college/university degree, college/university degree), Townsend deprivation index (continuous), living with partner (yes/no), ethnicity (European, South Asian, African Caribbean, other), employment (sedentary work, some standing and no heavy work, heavy manual work, not in employment, retired), transportation (passive, walking, cycling, working from home), smoking (never, former, current), alcohol intake (never, former, current-<3 times/week, current->3 times/week), diet quality index (0, 1, 2-3), family history of diabetes, CVD, or cancer (yes/no), diabetes status was self-reported (yes/no), depression (yes/no), loneliness (yes/no), pre-existing CVD, pre-existing cancer, and diabetes duration (continuous), and body mass index (continuous).

MET: metabolic equivalent, CVD: cardiovascular disease

Supplementary Figure 5. Leisure-time physical activity and nephropathy stratified by participant characteristics

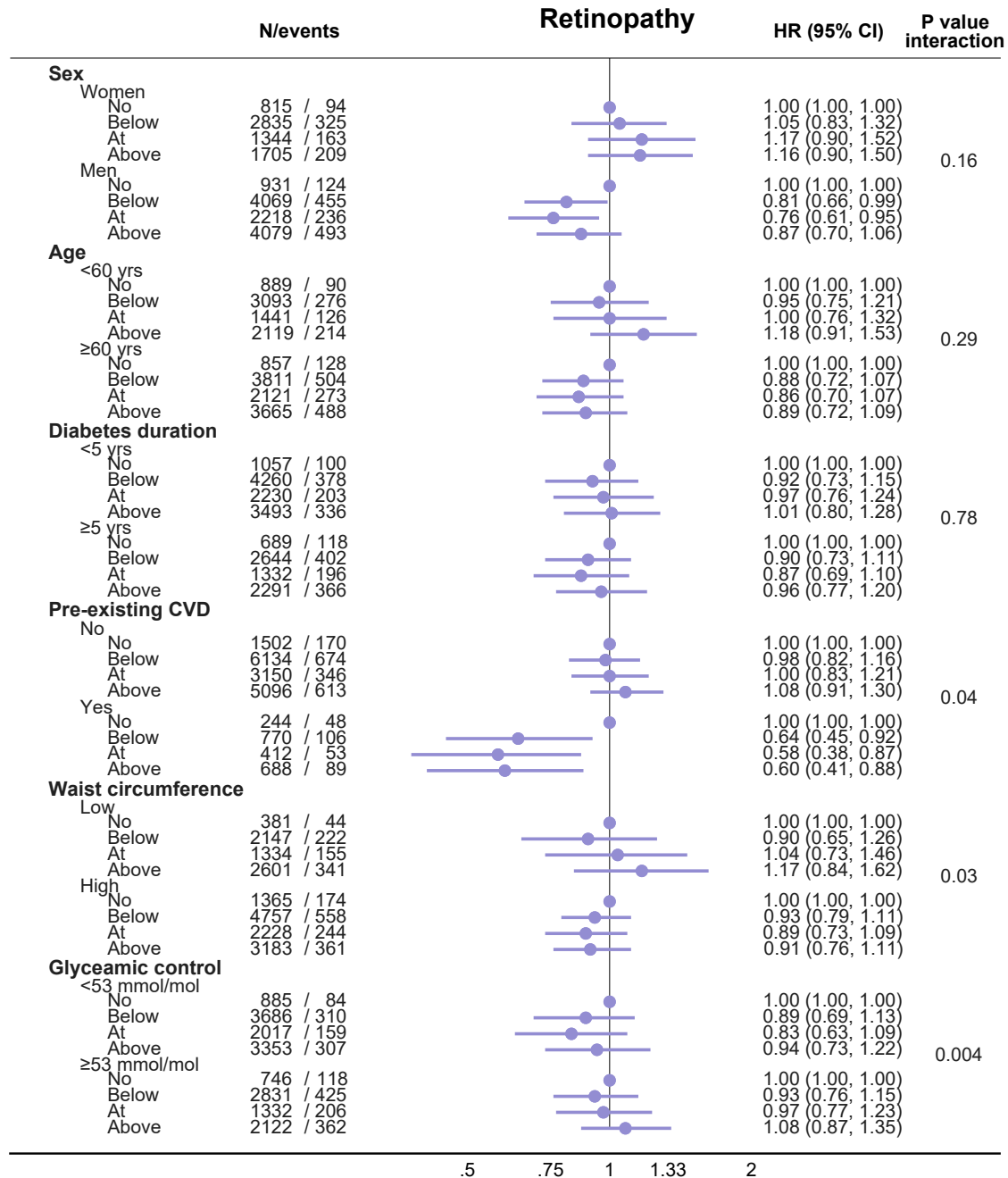


Categories of leisure-time physical activity defined as; none (0 MET-hrs/week), below recommendation (>0 to 7.49 MET-hrs/week), at recommendation (7.5-14.9 MET-hrs/week), and above recommendation (≥15 MET-hrs/week). Low waist circumference defined as <88/102 cm for women/men

Estimates were adjusted for model 3 including sex, age (timescale), education (no qualifications, qualifications - not college/university degree, college/university degree), Townsend deprivation index (continuous), living with partner (yes/no), ethnicity (European, South Asian, African Caribbean, other), employment (sedentary work, some standing and no heavy work, heavy manual work, not in employment, retired), transportation (passive, walking, cycling, working from home), smoking (never, former, current), alcohol intake (never, former, current-<3 times/week, current->3 times/week), diet quality index (0, 1, 2-3), family history of diabetes, CVD, or cancer (yes/no), diabetes status was self-reported (yes/no), depression (yes/no), loneliness (yes/no), pre-existing CVD, pre-existing cancer, and diabetes duration (continuous), and body mass index (continuous).

MET: metabolic equivalent, CVD: cardiovascular disease

Supplementary Figure 6. Leisure-time physical activity and retinopathy stratified by participant characteristics



Categories of leisure-time physical activity defined as; none (0 MET-hrs/week), below recommendation (>0 to 7.49 MET-hrs/week), at recommendation (7.5-14.9 MET-hrs/week), and above recommendation (≥15 MET-hrs/week). Low waist circumference defined as <88/102 cm for women/men

Estimates were adjusted for model 3 including sex, age (timescale), education (no qualifications, qualifications - not college/university degree, college/university degree), Townsend deprivation index (continuous), living with partner (yes/no), ethnicity (European, South Asian, African Caribbean, other), employment (sedentary work, some standing and no heavy work, heavy manual work, not in employment, retired), transportation (passive, walking, cycling, working from home), smoking (never, former, current), alcohol intake (never, former, current-<3 times/week, current->3 times/week), diet quality index (0, 1, 2-3), family history of diabetes, CVD, or cancer (yes/no), diabetes status was self-reported (yes/no), depression (yes/no), loneliness (yes/no), pre-existing CVD, pre-existing cancer, and diabetes duration (continuous), and body mass index (continuous).

MET: metabolic equivalent, CVD: cardiovascular disease

Supplementary Table 7. Sensitivity analyses, adjusted hazard ratios of leisure-time physical activity and microvascular complications.

	Total N/events	No leisure-time physical activity	Below recommendations (>0-7.49 MET-hrs/week)	At recommendations (7.5-14.9 MET-hrs/week)	Above recommendations (≥15 MET-hrs/week)
Neuropathy					
Main analysis	18077 / 672	1 [reference]	0.71 (0.56, 0.90)	0.73 (0.56, 0.96)	0.67 (0.52, 0.87)
Never smokers	8407 / 271	1 [reference]	0.54 (0.38, 0.78)	0.63 (0.42, 0.95)	0.50 (0.33, 0.74)
No history of cancer	16404 / 615	1 [reference]	0.71 (0.55, 0.91)	0.74 (0.55, 0.98)	0.64 (0.49, 0.85)
Excluding individuals with less certain type 2 diabetes*	17757 / 653	1 [reference]	0.72 (0.57, 0.92)	0.72 (0.54, 0.95)	0.66 (0.51, 0.87)
Left-censoring first 3 years of follow-up	17757 / 606	1 [reference]	0.70 (0.54, 0.90)	0.73 (0.55, 0.97)	0.68 (0.52, 0.89)
Fine-Gray competing risk model	18077 / 672	1 [reference]	0.72 (0.56, 0.91)	0.75 (0.57, 0.98)	0.68 (0.52, 0.88)
Nephropathy					
Main analysis	18067 / 1839	1 [reference]	0.79 (0.68, 0.92)	0.80 (0.67, 0.95)	0.80 (0.68, 0.95)
Never smokers	8399 / 716	1 [reference]	0.73 (0.57, 0.93)	0.82 (0.62, 1.07)	0.77 (0.59, 1.00)
No history of cancer	16395 / 1640	1 [reference]	0.78 (0.66, 0.91)	0.78 (0.65, 0.93)	0.80 (0.67, 0.95)
Excluding individuals with less certain type 2 diabetes*	17746 / 1799	1 [reference]	0.80 (0.69, 0.93)	0.80 (0.68, 0.96)	0.81 (0.69, 0.95)
Left-censoring first 3 years of follow-up	17771 / 1726	1 [reference]	0.83 (0.71, 0.97)	0.84 (0.70, 1.00)	0.83 (0.70, 0.98)
Fine-Gray competing risk model	18067 / 1839	1 [reference]	0.79 (0.68, 0.92)	0.80 (0.68, 0.95)	0.81 (0.68, 0.95)
Retinopathy					
Main analysis	17996 / 2099	1 [reference]	0.91 (0.78, 1.06)	0.91 (0.77, 1.08)	0.98 (0.84, 1.15)
Never smokers	8361 / 976	1 [reference]	0.93 (0.75, 1.17)	0.97 (0.75, 1.25)	0.99 (0.78, 1.26)
No history of cancer	16327 / 1891	1 [reference]	0.92 (0.78, 1.08)	0.90 (0.76, 1.08)	0.96 (0.81, 1.14)
Excluding individuals with less certain type 2 diabetes*	17677 / 2046	1 [reference]	0.92 (0.79, 1.07)	0.91 (0.77, 1.08)	0.99 (0.84, 1.16)
Left-censoring first 3 years of follow-up	17596 / 1890	1 [reference]	0.91 (0.78, 1.07)	0.92 (0.77, 1.10)	0.96 (0.81, 1.14)
Fine-Gray competing risk model	17996 / 2099	1 [reference]	0.92 (0.79, 1.07)	0.92 (0.78, 1.09)	1.00 (0.85, 1.17)

*Individuals classified as 'possible type 2 diabetes' from Eastwood Algorithm and HbA1c <48 mmol/mol. HRs with 95% confidence intervals.

Estimates were adjusted for model 3 including sex, age (timescale), education (no qualifications, qualifications - not college/university degree, college/university degree), Townsend deprivation index (continuous), living with partner (yes/no), ethnicity (European, South Asian, African Caribbean, other), employment (sedentary work, some standing and no heavy work, heavy manual work, not in employment, retired), transportation (passive, walking, cycling, working from home), smoking (never, former, current), alcohol intake (never, former, current-<3 times/week, current->3 times/week), diet quality index (0, 1, 2-3), family history of diabetes, CVD, or cancer (yes/no), diabetes status was self-reported (yes/no), depression (yes/no), loneliness (yes/no), pre-existing CVD, pre-existing cancer, and diabetes duration (continuous), and body mass index (continuous).

MET: metabolic equivalent

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