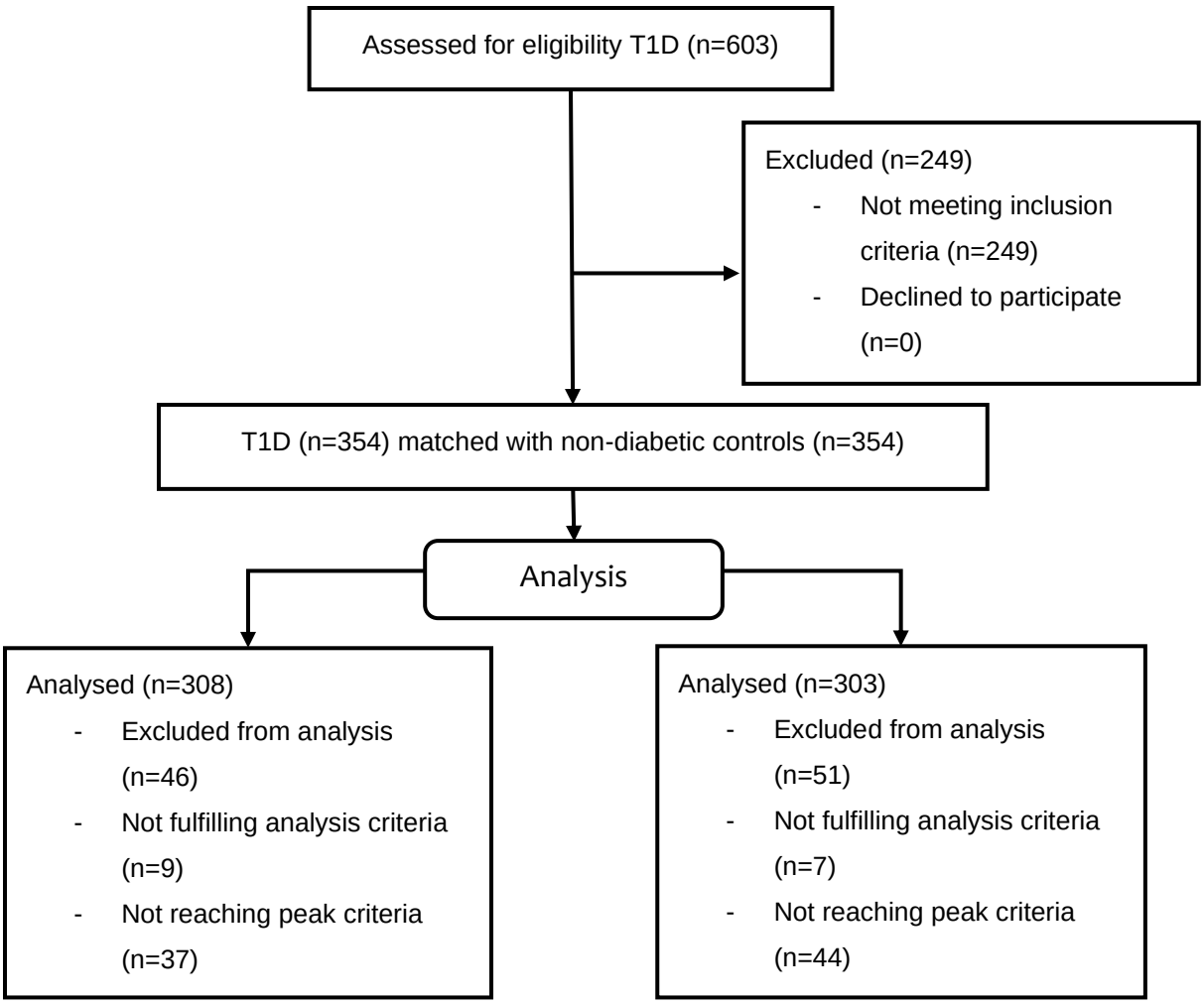

Figure S1: Flow diagram data inclusion and analysis of data

Table S1– Medication of individuals with T1DM

ACE inhibitors	PPI	Progestogen	Estrogen	Cortisone	NSAID	Antidepressants	Thyroid Hormones	Antihistamines
16	7	9	6	1	19	3	10	7

ACE-inhibitor: Angiotensin-converting enzyme inhibitor. PPI: Proton pump inhibitor. NSAID: Non-steroidal anti-inflammatory drug.

24% of all participants with T1DM were taking any above the abovementioned medication. No individual in the control group was on any medication.

Table S2–Parameters of physiological performance during cardio-pulmonary exercise testing in individuals with type 1 diabetes and healthy controls

	T1D	Controls	p-value
VO_2 as % VO_{2peak}			
VT_1	42.1 [36.3; 48.7]	39.7 [35.5; 44.0]	0.002
VT_2	74.4 [68.1; 79.3]	73.5 [68.9; 77.6]	0.30
HR as % HR_{peak}			
VT_1	61.9 [57.7; 65.4]	62.2 [58.2; 67.0]	0.07
VT_2	83.9 [80.7; 87.0]	85.0 [81.1; 88.4]	0.02
P as % P_{peak}			
VT_1	33.3 [30.8;35.3]	31.3 [28.6; 33.8]	<0.001
VT_2	70.4 [67.7; 72.5]	69.4 [67.2; 71.4]	0.001
Oxygen Economy (mL/min/W)			
VT_1	14.74 [12.93; 16.89]	16.11 [14.14; 19.19]	<0.001
VT_2	12.06 [10.91; 13.17]	13.42 [12.41; 14.61]	<0.001
Peak	11.98 ± 2.05	12.77 [11.82; 13.88]	<0.001
Ventilation (L/min)			
Pre-Exercise	12.53 ± 3.34	10.63 [8.63; 12.96]	0.82
VT_1	24.00 [20.89; 28.34]	27.98 [22.33; 32.13]	0.20
VT_2	47.00 [38.00; 58.00]	57.70 ± 14.01	<0.001
Peak	88.20 [69.83; 108.70]	112.9 [88.52;129.9]	<0.001
Respiratory Exchange Ratio			
Pre-Exercise	0.85 ± 0.07	0.84 [0.78; 0.90]	0.90
VT_1	0.85 ± 0.08	0.83 ± 0.07	0.01
VT_2	1.03 ± 0.08	0.99 ± 0.06	<0.001
Peak	1.21 ± 0.09	1.16 ± 0.07	<0.001
EQO_2			
Pre-Exercise	25.94 [23.57; 28.19]	24.46 [22.04; 27.25]	0.037
VT_1	22.30 [20.10; 24.62]	20.52 [18.69; 22.82]	<0.001
VT_2	25.48 [23.10; 27.98]	23.95 [21.62; 26.08]	<0.001
Peak	34.30 [30.74; 38.79]	33.38 [30.48; 36.93]	0.299
$EQCO_2$			
Pre-Exercise	30.61 [28.10; 33.27]	28.51 [26.37; 31.75]	<0.001
VT_1	26.44 [24.10; 28.20]	24.46 [22.72; 26.98]	<0.001
VT_2	24.49 [22.56; 26.61]	23.88 [22.20; 26.01]	0.42
Peak	28.51 [25.82; 31.35]	29.18 [26.98; 31.97]	0.38
$PETO_2$ (mmHg)			
Pre-Exercise	109.70 [106.20; 113.00]	107.60 ± 6.81	0.06
VT_1	102.40 [98.34; 106.30]	98.24 ± 7.07	<0.001
VT_2	107.00 [103.20; 110.80]	104.80 ± 6.46	0.004
Peak	117.2 ± 5.57	119.00 ± 4.91	0.01
$PETCO_2$ (mmHg)			
Pre-Exercise	34.36 [31.86; 36.20]	35.23 [32.42; 37.91]	0.52
VT_1	40.10 ± 3.65	41.49 [38.79; 44.28]	0.01
VT_2	42.40 ± 4.62	42.55 [39.42; 45.76]	0.75
Peak	36.94 ± 5.40	33.68 [30.77; 36.89]	<0.001

Data are shown as mean ± standard deviation or median [interquartile range] dependent on distribution of the data. VT_1: Ventilatory threshold 1. VT_2: Ventilatory threshold 2. mL: Milliliter. L/min: Liter per minute. Kg: Kilogram. W: Watt.VO_2: Volume of oxygen. EQO_2: Oxygen equivalent. $EQCO_2$: Carbon dioxide equivalent. $PETO_2$: End-tidal oxygen tension. $PETCO_2$: End-tidal carbon dioxide tension.

Females:

Subgroup analyses between females with T1D and healthy females are shown in table S2. In this analysis 93 females with T1D (age: 34 ± 11 years, BMI: 22.9 [21.1; 25.7] kg/m^2) and 88 healthy females (age: 30 ± 13 years, BMI: 21.5 [20.5; 23.9] kg/m^2) were included.

Table S3–Parameters of physiological performance during cardio-pulmonary exercise testing in females with type 1 diabetes and healthy females

	T1D	Controls	p-value
n	93	88	
K_{HR}	0.45 ± 1.25	0.90 ± 1.1	0.01
Absolute VO_2 (L/min)			
Pre-Exercise	0.4 ± 0.1	0.2 [0.2; 0.3]	0.61
VT_1	0.8 ± 0.2	0.9 ± 0.2	0.06
VT_2	1.3 ± 0.1	1.7 ± 0.3	<0.001
Peak	1.8 ± 0.4	2.2 ± 0.4	<0.001
Relative VO_2 (mL/Kg/min)			
Pre-Exercise	5.6 ± 1.6	4.9 ± 1.1	0.90
VT_1	12.9 ± 3.3	15.8 ± 3.0	<0.001
VT_2	20.6 ± 4.7	27.8 ± 5.9	<0.001
Peak	27.4 ± 6.9	36.9 ± 8.7	<0.001
VO_2R			
VT_1	7.4 ± 2.6	10.8 ± 3.1	<0.001
VT_2	14.9 ± 4.5	22.9 ± 6.3	<0.001
Peak	21.9 ± 6.7	32.9 [25.8; 38.4]	<0.001
HR (bpm)			
Pre-Exercise	89 ± 13	89 [78; 103]	0.55
VT_1	113 ± 13	121 ± 16	0.001
VT_2	150 ± 15	159 ± 16	<0.001
Peak	175 ± 13	186 [175; 192]	0.002
HRR (bpm)			
VT_1	24 ± 7	29 ± 11	0.03
VT_2	61 ± 14	68 ± 15	0.005
Peak	87 ± 14	92 ± 16	0.06
O_2 pulse (mL/beat)			
Pre-Exercise	4.3 ± 1.6	4.2 ± 1.6	0.99
VT_1	7.4 [6.3; 9.5]	9.8 ± 3.3	<0.001
VT_2	9.0 [7.7; 11.1]	12.1 [10.0; 16.0]	<0.001
Peak	9.6 [8.6; 12.7]	14.2 [11.5; 18.8]	<0.001
Absolute Power (W)			
VT_1	55 [47; 60]	60 [50; 66]	0.66
VT_2	115 [97; 131]	125 [108; 155]	<0.001
Peak	160 [138; 186]	185 [155; 215]	<0.001
Relative Power (W/Kg)			

VT_1	0.8 ± 0.2	0.9 ± 0.3	0.14
VT_2	1.7 ± 0.4	2.1 ± 0.5	<0.001
Peak	2.5 ± 0.6	3.0 ± 0.7	<0.001
VO_2 in % VO_{2peak}			
VT_1	48.4 ± 11.0	43.6 ± 8.1	<0.001
VT_2	75.5 ± 9.4	75.3 ± 6.3	0.84
HR in % HR_{peak}			
VT_1	64.2 ± 6.1	65.7 ± 6.3	0.09
VT_2	85.2 ± 4.4	86.6 ± 4.4	0.03
P given as % P_{peak}			
VT_1	34.1 [32.4; 36.5]	32.5 [29.6; 34.8]	<0.001
VT_2	70.2 [68.0; 72.2]	70.0 [67.1; 71.4]	0.10
Oxygen Economy (mL/min/W)			
VT_1	15.6 [13.9; 17.4]	16.0 [14.0; 18.2]	0.005
VT_2	12.1 [10.9; 12.9]	13.3 [12.0; 14.3]	<0.001
Peak	11.2 [10.5; 12.2]	12.0 [11.3; 13.2]	0.006
Ventilation (L/min)			
Pre-Exercise	11.6 ± 3.3	9.3 [7.3; 12.0]	0.73
VT_1	21.0 [18.2; 26.0]	22.0 [19.6; 26.9]	0.89
VT_2	38.4 ± 8.8	45.1 ± 8.3	<0.001
Peak	69.9 ± 22.7	80.1 ± 14.5	<0.001
Respiratory Exchange Ratio			
Pre-Exercise	0.83 ± 0.07	0.85 ± 0.10	0.93
VT_1	0.83 ± 0.08	0.83 ± 0.07	0.99
VT_2	1.01 ± 0.08	0.99 ± 0.06	0.60
Peak	1.19 ± 0.08	1.16 ± 0.07	0.02
EQO_2			
Pre-Exercise	26.2 [23.8; 28.2]	26.5 ± 4.5	0.98
VT_1	23.1 ± 3.2	22.3 ± 3.1	0.58
VT_2	26.6 ± 3.7	25.4 ± 3.5	0.24
Peak	35.6 ± 6.3	34.5 ± 5.9	0.34
$EQCO_2$			
Pre-Exercise	31.3 ± 4.6	30.4 [28.0; 33.2]	0.92
VT_1	27.8 [25.6; 29.1]	26.7 ± 3.1	0.21
VT_2	26.3 ± 2.9	25.4 [23.5; 27.0]	0.47
Peak	30.0 ± 4.5	29.1 [26.7; 31.8]	0.94
$PETO_2$ (mmHg)			
Pre-Exercise	112.0 ± 4.5	111.2 ± 5.9	0.80
VT_1	105.3 ± 4.9	101.4 ± 6.5	<0.001
VT_2	109.4 ± 5.8	107.6 ± 5.7	0.16
Peak	118.9	119.6 ± 4.7	0.93
$PETCO_2$ (mmHg)			
Pre-Exercise	32.6 [29.9; 34.9]	32.9 ± 3.4	0.79
VT_1	37.5 ± 3.0	38.9 ± 3.7	0.09
VT_2	39.3 [36.6; 42.3]	40.3 ± 4.5	0.84
Peak	35.2 ± 4.7	33.5 ± 4.8	0.05

Data are shown as mean ± standard deviation or median [interquartile range] dependent on distribution of the data. VT_1: Ventilatory threshold 1. VT_2: Ventilatory threshold 2. mL: Milliliter. L/min: Liter per minute. Kg: Kilogram. W: Watt. VO_2: Volume of oxygen. EQO_2: Oxygen equivalent. $EQCO_2$: Carbon dioxide equivalent. $PETO_2$: End-tidal oxygen tension. $PETCO_2$: End-tidal carbon dioxide tension.

Males:

Subgroup analyses between males with T1D and healthy males are shown in table S3. In this analysis 210 males with T1D (age: 32 [26; 41] years, BMI: 24.6 [22.7; 26.4] kg/m^2) and 220 healthy males (age: 36 [23; 44] years, BMI: 24.0 [22.5; 27.0] kg/m^2) were included.

Table S4–Parameters of physiological performance during cardio-pulmonary exercise testing in males with type 1 diabetes and healthy males

	T1D	Controls	p-value
n	210	220	
K_{HR}	-0.08 [-0.81; 0.93]	0.50 [-0.47; 1.25]	0.003
Absolute VO_2 (L/min)			
Pre-Exercise	0.4 ± 0.1	0.4 ± 0.1	0.89
VT_1	1.1 [0.9; 1.3]	1.4 ± 0.3	<0.001
VT_2	2.0 [1.7; 2.4]	2.6 ± 0.6	<0.001
Peak	2.8 ± 0.7	3.6 ± 0.7	<0.001
Relative VO_2 (mL/Kg/min)			
Pre-Exercise	5.4 [4.7; 6.4]	5.1 ± 1.3	0.85
VT_1	13.7 [11.2; 16.3]	16.9 [14.2; 20.3]	<0.001
VT_2	24.8 [20.9; 30.4]	32.6 ± 8.1	<0.001
Peak	35.3 [30.0; 40.7]	45.1 [36.7; 52.5]	<0.001
VO_2R			
VT_1	8.5 [6.0; 10.5]	12.2 ± 4.1	<0.001
VT_2	19.9 [14.9; 24.0]	27.5 ± 7.7	<0.001
Peak	29.9 [23.9; 34.9]	39.9 ± 9.4	<0.001
HR (bpm)			
Pre-Exercise	83 ± 12	83 ± 14	0.97
VT_1	108 [100; 116]	113 ± 15	0.05
VT_2	149 ± 15	153 ± 16	0.02
Peak	179 ± 12	183 ± 13	0.09
HRR (bpm)			
VT_1	25 [18; 31]	29 ± 9	0.002
VT_2	65 ± 15	70 ± 14	<0.001
Peak	96 ± 13	99 ± 14	0.006
O_2 pulse (mL/beat)			
Pre-Exercise	5.5 ± 1.4	5.5 [4.7; 6.8]	0.93
VT_1	10.5 [8.6; 12.0]	13.5 [11.3; 16.3]	<0.001
VT_2	13.9 [11.7; 15.9]	19.4 ± 5.1	<0.001
Peak	15.9 [13.4; 18.2]	21.9 [18.7; 25.4]	<0.001
Absolute Power (W)			
VT_1	77 ± 18	84 ± 21	0.12
VT_2	160 [140; 200]	190 [160; 220]	<0.001
Peak	240 [200; 276]	275 [230; 319]	<0.001
Relative Power (W/Kg)			

VT_1	1.0 [0.8; 1.1]	1.1 ± 0.3	0.29
VT_2	2.1 [1.8; 2.5]	2.4 [1.9; 2.7]	<0.001
Peak	2.9 [2.6; 3.5]	3.4 [2.8; 4.1]	<0.001
VO_2 in % VO_{2peak}			
VT_1	39.8 [34.8; 45.5]	39.1 [35.2; 43.0]	0.12
VT_2	72.5 ± 8.5	72.8 ± 7.7	0.63
HR in % HR_{peak}			
VT_1	60.8 ± 5.7	61.6 ± 6.0	0.16
VT_2	82.9 ± 4.8	83.6 ± 5.6	0.26
P given as % P_{peak}			
VT_1	32.6 [30.0; 34.3]	30.8 [28.3; 33.3]	<0.001
VT_2	70.6 [67.6; 72.5]	69.4 [67.2; 71.4]	0.002
Oxygen Economy (mL/min/W)			
VT_1	14.5 [12.6; 16.6]	16.2 [14.2; 19.5]	<0.001
VT_2	12.1 ± 2.2	13.5 [12.5; 14.7]	<0.001
Peak	11.8 ± 1.6	13.1 [12.1; 14.0]	<0.001
Ventilation (L/min)			
Pre-Exercise	12.9 ± 3.2	11.6 ± 3.7	0.80
VT_1	25.5 [22.0; 29.0]	29.7 ± 6.6	0.06
VT_2	52.0 [44.0; 61.6]	62.7 ± 12.6	<0.001
Peak	95.5 [80.5; 116.4]	123.4 ± 21.2	<0.001
Respiratory Exchange Ratio			
Pre-Exercise	0.85 ± 0.07	0.84 [0.79; 0.89]	0.94
VT_1	0.85 [0.81; 0.91]	0.83 ± 0.06	<0.001
VT_2	1.04 ± 0.07	0.99 [0.95; 1.03]	<0.001
Peak	1.22 ± 0.08	1.15 ± 0.06	<0.001
EQO_2			
Pre-Exercise	26.2 ± 3.7	23.7 [21.5; 26.7]	0.001
VT_1	22.4 ± 3.4	20.1 [18.4; 21.2]	<0.001
VT_2	25.2 ± 3.7	23.6 ± 3.6	0.001
Peak	33.8 [30.3; 38.1]	33.9 ± 5.4	0.72
$EQCO_2$			
Pre-Exercise	30.8 ± 3.8	27.8 [25.6; 30.8]	0.35
VT_1	24.1 [23.6; 27.5]	23.8 [22.2; 26.2]	0.99
VT_2	24.1 ± 2.7	23.5 [21.8; 25.1]	0.91
Peak	28.5 [25.7; 30.4]	29.4 ± 3.9	0.90
$PETO_2$ (mmHg)			
Pre-Exercise	108.3 [104.4; 111.7]	106.0 [102.1; 109.7]	0.23
VT_1	100.7 ± 6.3	96.6 [92.9; 101.2]	<0.001
VT_2	106.2 [102; 110]	104.0 [98.8; 108.2]	0.01
Peak	116.2 [112.8; 120.2]	118.1 ± 9.2	0.09
$PETCO_2$ (mmHg)			
Pre-Exercise	34.8 ± 3.5	35.6 ± 3.8	0.40
VT_1	41.3 ± 3.3	42.7 [39.7; 45.2]	0.04
VT_2	43.6 ± 4.3	43.3 ± 4.5	0.99
Peak	37.7 ± 5.5	33.8 [31.2; 36.7]	<0.001

Data are shown as mean ± standard deviation or median [interquartile range] dependent on distribution of the data. VT_1: Ventilatory threshold 1. VT_2: Ventilatory threshold 2. mL: Milliliter. L/min: Liter per minute. Kg: Kilogram. W: Watt. VO_2: Volume of oxygen. EQO_2: Oxygen equivalent. $EQCO_2$: Carbon dioxide equivalent. $PETO_2$: End-tidal oxygen tension. $PETCO_2$: End-tidal carbon dioxide tension.

Table S5–Parameters of physiological performance during cardio-pulmonary exercise testing in a subgroup of individuals with type 1 diabetes and healthy individuals matched for BMI, age and sex (S6.1)

	T1D	Controls	p-value
n	96	96	
K_{HR}	0.08 ± 1.21	0.36 ± 1.2	0.03
Absolute VO_2 (L/min)			
Pre-Exercise	0.5 ± 0.1	0.5 ± 0.1	0.99
VT_1	1.1 ± 0.3	1.4 ± 0.3	0.26
VT_2	1.4 ± 0.3	1.9 ± 0.5	0.02
Peak	2.2 ± 0.4	2.5 ± 0.3	0.006
Relative VO_2 (mL/Kg/min)			
Pre-Exercise	6.6 ± 1.4	7.0 ± 1.3	0.90
VT_1	12.8 ± 3.2	15.2 ± 3.8	0.006
VT_2	20.9 ± 5.9	25.1 ± 5.8	<0.001
Peak	28.4 ± 8.1	35.8 ± 8.7	<0.001
VO_2R			
VT_1	6.1 ± 2.9	8.0 ± 3.5	<0.001
VT_2	14.5 ± 6.1	17.9 ± 5.6	<0.001
Peak	22.6 ± 7.9	28.8 [20.7; 30.3]	<0.001
HR (bpm)			
Pre-Exercise	84 [76;91]	77 [68; 88]	0.08
VT_1	106 ± 13	100 [89; 110]	0.05
VT_2	140 ± 18	136 [122; 148]	0.34
Peak	168 ± 17	169 ± 14	0.89
HRR (bpm)			
VT_1	21 ± 8	21 [16; 26]	0.98
VT_2	55 ± 14	56 ± 13	0.97
Peak	86 [77; 94]	89 [81; 100]	0.02
O_2 pulse (mL/beat)			
Pre-Exercise	5.6 ± 1.5	7.3 ± 2.0	0.001
VT_1	9.5 ± 3.2	11.7 ± 3.2	<0.001
VT_2	11.9 ± 3.9	14.4 ± 3.9	<0.001
Peak	13.2 ± 4.2	15.1 [12.5; 18.3]	0.001
Absolute Power (W)			
VT_1	65 [56; 80]	78 ± 19	0.26
VT_2	141 ± 43	156 ± 39	0.02
Peak	202 ± 60	219 ± 56	0.006
Relative Power (W/Kg)			
VT_1	0.8 ± 0.2	0.9 ± 0.3	0.49
VT_2	1.7 ± 0.6	1.9 ± 0.6	0.18
Peak	2.3 ± 0.9	2.6 ± 0.9	<0.001
VO_2 in % VO_{2peak}			
VT_1	45.4 [38.7; 50.3]	45.3 [41.4; 53.0]	0.27
VT_2	73.2 [69.5; 78.9]	78.7 [73.6; 83.5]	<0.001
HR in % HR_{peak}			
VT_1	62.7 [59.4; 67.4]	58.4 [55.6; 64.5]	<0.001
VT_2	82.8 [80.4; 86.4]	80.8 [77.2; 84.8]	<0.001
P given as % P_{peak}			
VT_1	34.2 [32.4; 36.3]	35.0 [32.9; 37.6]	0.04
VT_2	70.5 [67.8; 72.2]	70.1 [68.6; 73.8]	0.03

Oxygen Economy (mL/min/W)			
VT_1	14.5 [12.6; 16.9]	14.8 [13.2; 16.3]	0.93
VT_2	11.0 [8.9; 12.2]	12.4 [11.7; 13.3]	<0.001
Peak	10.9 [8.1; 12.0]	11.3 [10.9; 11.9]	0.90
Ventilation (L/min)			
Pre-Exercise	14.5 [12.0; 16.4]	17.9 [14.5; 20.0]	0.37
VT_1	24.8 ± 5.1	31.0 [24.0; 34.3]	0.11
VT_2	45 ± 12.1	55.5 ± 13.5	<0.001
Peak	80 ± 24.2	90 [76.0; 119.0]	<0.001
Respiratory Exchange Ratio			
Pre-Exercise	0.87 ± 0.08	0.81 [0.76; 0.85]	<0.001
VT_1	0.85 ± 0.08	0.79 [0.75; 0.82]	<0.001
VT_2	1.02 ± 0.08	1.0 [0.93; 1.05]	0.03
Peak	1.20 [1.10; 1.30]	1.19 ± 0.08	0.84
EQO_2			
Pre-Exercise	26.1 [24.0; 28.1]	27.1 [24.9; 30.7]	0.08
VT_1	22.5 [20.6; 24.9]	22.6 [21.0; 25.1]	0.98
VT_2	25.0 [22.9; 28.9]	26.6 [24.0; 29.5]	0.75
Peak	33.3 [30.1; 37.8]	36.4 [32.5; 41.1]	0.005
$EQCO_2$			
Pre-Exercise	30.5 ± 6.7	33.2 [31.4; 36.2]	<0.001
VT_1	27.0 [24.6; 28.8]	29.3 [26.9; 31.1]	<0.001
VT_2	24.7 [23.1; 27.5]	27.4 [24.4; 29.2]	0.009
Peak	28.1 [26.2; 31.4]	31.3 [28.1; 33.9]	0.001
$PETO_2$ (mmHg)			
Pre-Exercise	111.3 ± 3.7	112.2 ± 5.9	0.81
VT_1	104.5 ± 5.2	105.6 ± 6.7	0.55
VT_2	108.5 ± 5.8	108.1 ± 6.3	0.99
Peak	117 ± 5.6	118.0 ±5.8	0.89
$PETCO_2$ (mmHg)			
Pre-Exercise	34.2 ± 3.4	31.7 [29.9; 33.3]	0.001
VT_1	39.3 ± 3.7	36.6 [34.6; 39.2]	0.001
VT_2	41.3 ± 4.9	39.9 [36.8; 43.3]	0.39
Peak	36.7 ± 5.4	36.0 [32.0; 38.9]	0.58

S5.1: Physical activity analysis for the matched subgroup analysis in table S5

	T1D	Controls	P value
Baecke Index	8.5 ± 1.4	8.9 ± 1.5	0.09
Sports Index	3.1 ± 0.9	3.3 ± 0.8	0.29
Leisure Index	3.1 ± 0.7	3.2 ± 0.8	0.44
Work Index	2.3 ± 0.5	2.4 ± 0.6	0.08

In comparison of the entire cohort shown in the manuscript vs. the subgroup of S5 and S5.1, median difference of relative VO_{2peak} (8.6 [1.1; 18.3] vs. 7.8 [0.6; 13.7] mL/Kg/min) (p=0.28), HR_{peak} (4 [-7; 15] to 0 [-15; 15] bpm) (p=0.74) and absolute power output (33 [-25; 93] to 15 [-25; 66] W) (p=0.12) was not significantly different.