Online Supplement: Methodology of systematic literature analysis and meta-analysis

Normal values of exercise pulmonary hemodynamics

Data sources and search strategy

We searched Pubmed (MEDLINE), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials from 01.01.2003 - 01.11.2020. We performed separate searches for mPAP, PAWP and PVR. The following Medical Subject Headings (MESH) were used: "healthy", "health*", "normal", "normative", "athletes" AND "exercise". For the analysis of mPAP we used the following additional MESH: „mean pulmonary arterial pressure (MESH)", „Pulmonary Arterial Pressure", „mPAP", „meanPAP", „mean pulmonary arterial pressure", „mean pulmonary artery pressure", „PAPm", „Pulmonary Artery Pressure", "Pulmonary Hypertension (MESH)", „Pulmonary Artery Hypertension", „Pulmonary Arterial Hypertension". For the PAWP analysis we used: „pulmonary arterial wedge pressure (MESH)", „pulmonary wedge pressure", „pulmonary artery wedge pressure", „PAWP", „Pulmonary Capillary Wedge Pressure", „pulmonary capillary pressure", „pulmonary artery occlusion pressure", „PAOP", „PCWP", „pulmonary arterial occlusion pressure", „pulmonary venous wedge pressure", „PVWP", „pulmonary venous pressure", „lung venous pressure" AND "Pulmonary Hypertension (MESH)", "Pulmonary Artery Hypertension", "Pulmonary Arterial Hypertension". For PVR analysis we used: „pulmonary vascular resistance (MESH)", „total pulmonary resistance", „PVR", „TPR", „total pulmonary vascular resistance" AND "Pulmonary Hypertension (MESH)", "Pulmonary Artery Hypertension", "Pulmonary Arterial Hypertension".

Study Selection

In total n=1069 studies were identified through database screening. N=547 remained after removing all duplicates and were screened. In n=62 studies, full text was assessed for eligibility. We only included original manuscripts with original data. N=51 studies were excluded due to several reasons (n=22 no exercise RHC; n=8 no baseline RHC; n=1 no original data; n=9 same subjects used; n=9 not healthy). In addition, we excluded studies that did not provide numerical data of pulmonary hemodynamics (eg: only graphical data)(n=1; [1]) and studies that measured CO by echocardiography and not by RHC (n=1; [2]). In total, n=11 studies were included in the qualitative and quantitative synthesis (see Supplement Figure 1: Flow-Chart). Of note, the zero reference level was provided only in a small number of studies (n=5). An overview of the included studies is provided in Supplement Table 1.

Excluded studies

Exclusion reason	Study
No exercise RHC in healthy	[1,3-23]
No baseline RHC values available	[24-31]
No original data	[32]
Same subjects used	[7,33-38] [160]
Claimed healthy but dyspnea patients	[39-47]
CO measured by Doppler	[48]
No mPAP	[49]

Outcomes

The primary outcome of interest was pulmonary hemodynamics in healthy subjects.

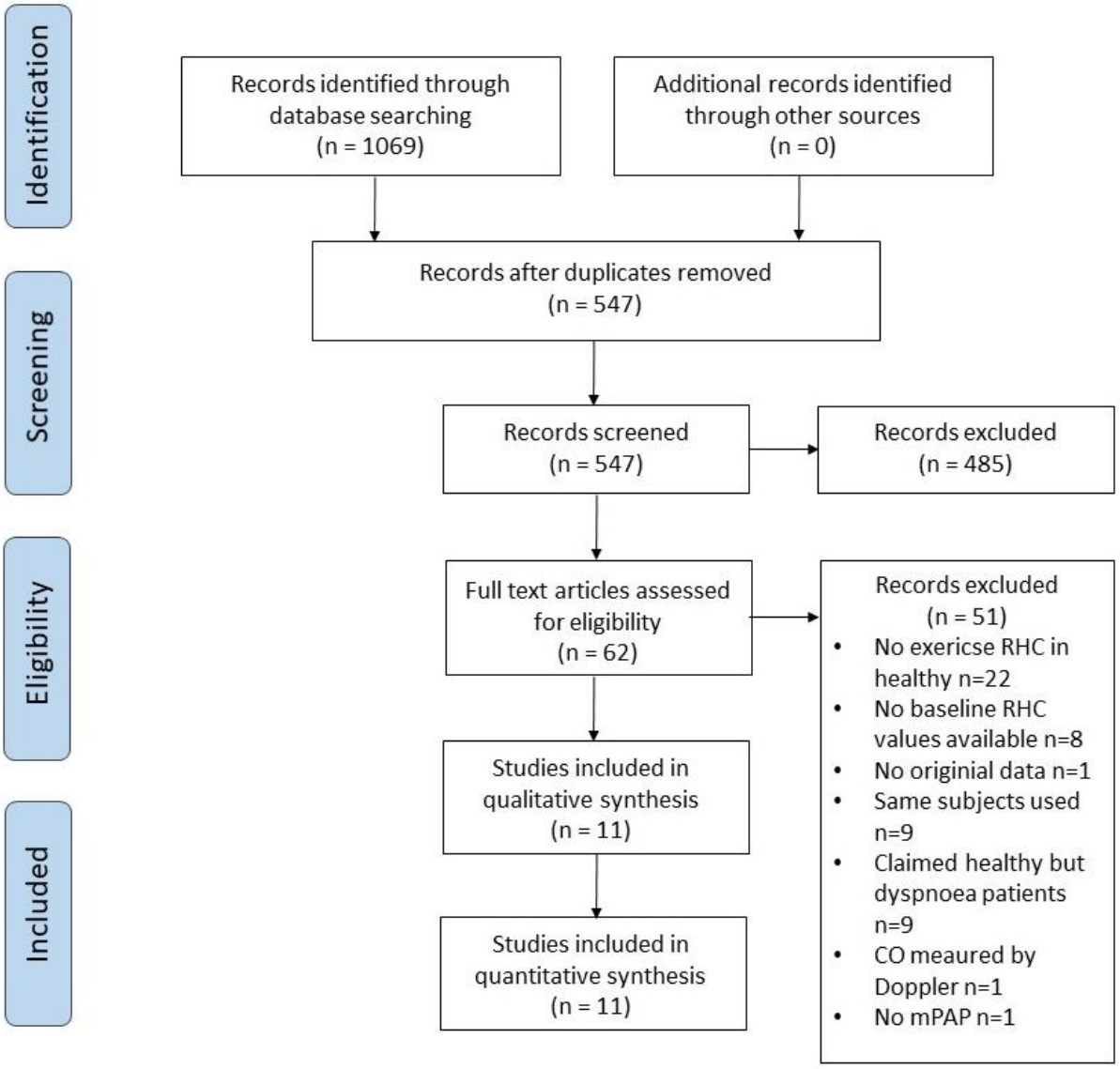
Data preparation

In the identified studies, data was reported differently. Some authors gave the mean values and the standard deviation of parameters for the whole group, others median and IQR, Q1, Q3 or 95% CI. Mean and SD were calculated from median and IQR with the formula described by Wan et al 2014 [50]. SD were also calculated from 95% CI. If only median and IQR were available, Q1 and Q3 were calculated as Q1 = median – (IQR/2) and Q3 = median + (IQR/2). In one study (Lewis et al. 2011), the SD of the RAP value at rest was reported as 0 probably due to approximation. To enable the estimation of the weighted means moderated by age, this value was replaced by 0.1. Furthermore, mean values of a number of parameters were not reported in some studies and had to be calculated using the following formulas: Height(m) = Square-root(Weight/BMI); BSA=Square-root(Height(cm)*Weight(Kg)/3600), this corresponds to the Mosteller Formula. Note that, if mean height and weight were not available, mean BSA was calculated by interpolating the mean values reported for normal weight and overweight in Verbraecken et al. [51]; CO = CI * BSA; CI = CO/BSA; PVR = (mPAP – PAWP)/CO; PVR = PVRI/BSA; TPG = mPAP – PAWP; TPR = mPAP/CO; PAC = (CO*1000/HR) / (sPAP-dPAP); Slope mPAP/CO = (mPAP max – mPAP rest) / (CO max – CO rest); Slope PAWP/CO = (PAWP max – PAWP rest) / (CO max – CO rest); Slope TPG/CO = (TPG max – TPG rest) / (CO max – CO rest). Slopes were only calculated when measurements at rest and during exercise were performed in the same body position. Please note that only mean values were calculated using the above-listed formulas. Standard deviations of the calculated variables (representing the “uncertainty” of the measure) depend upon the uncertainties of the variables used in the formula. The standard deviation of the output variables was therefore calculated with derivatives, using the R package “errors” and following the error propagation method

described by Ucar, Pebesma, & Azcorra [52].” In the case of BSA values obtained by interpolation, the corresponding SDs were computed from the mean of the available SDs.

Measurements in the supine position were grouped as supine. Measurements in the semi-supine or semi-upright position were grouped as upright.

Figure S1: Flow-Chart for normal value



Prognostic value of exercise pulmonary hemodynamics

Data sources and search strategy

We searched Pubmed (MEDLINE), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials from 1945 through 01.11.2020 for English-language, peer-reviewed publications. For mPAP, PAWP and PVR we performed independent systematic literature analyses. The following Medical Subject Headings (MESH) were used: „prognosis“, „outcome“, „death“, „prognos*“, „survival“, as well as „Pulmonary Hypertension (MESH)“, „Pulmonary Artery Hypertension“, „Pulmonary Arterial Hypertension“, AND “exercise” (MESH). For the analysis of mPAP we used the following additional MESH: „mean pulmonary arterial pressure (MESH)“, „Pulmonary Arterial Pressure“, „mPAP“, „meanPAP“, „mean pulmonary arterial pressure“, „mean pulmonary artery pressure“, „PAPm“, „Pulmonary Artery Pressure“, “Pulmonary Hypertension (MESH)“, „Pulmonary Artery Hypertension“, „Pulmonary Arterial Hypertension“. For the PAWP analysis we used: „pulmonary arterial wedge pressure (MESH)“, „pulmonary wedge pressure“, „pulmonary artery wedge pressure“, „PAWP“, „Pulmonary Capillary Wedge Pressure“, „pulmonary capillary pressure“, „pulmonary artery occlusion pressure“, „PAOP“, „PCWP“, „pulmonary arterial occlusion pressure“, „pulmonary venous wedge pressure“, „PVWP“, „pulmonary venous pressure“, „lung venous pressure“ AND “Pulmonary Hypertension (MESH)”, “Pulmonary Artery Hypertension”, “Pulmonary Arterial Hypertension”. For PVR analysis we used: „pulmonary vascular resistance (MESH)“, „total pulmonary resistance“, „PVR“, „TPR“, „total pulmonary vascular resistance“ AND “Pulmonary Hypertension (MESH)”, “Pulmonary Artery Hypertension”, “Pulmonary Arterial Hypertension”.

Excluded studies

Exclusion reason	**Study**
Endpoint other than mortality	[14,23,56-90]
No original data	[91-98]
No exercise RHC	[99-127]
Editorial/Abstract	[128-137]

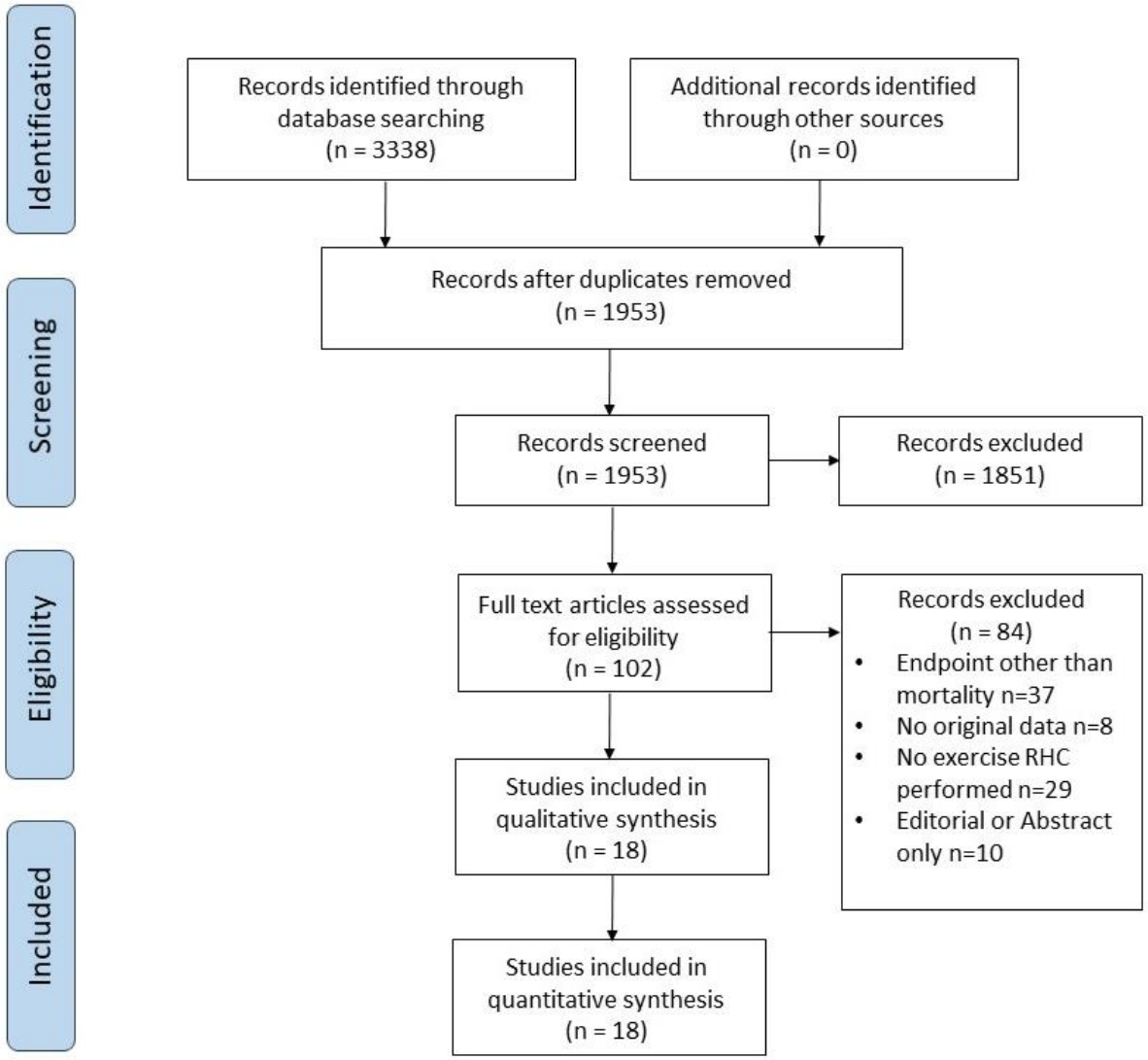
Outcomes

The primary outcome was all-cause mortality.

Statistical analysis

Prognostic studies are provided descriptively in the main document.

Figure S2: Flow-Chart for prognostic studies



Diagnostic value of exercise pulmonary hemodynamics

Data sources and search strategy

We searched Pubmed (MEDLINE), EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials from 1945 through 01.11.2020 for English-language, peer-reviewed publications. For mPAP, PAWP and PVR we performed independent systematic literature analyses. The following Medical Subject Headings (MESH) were used: "Differential diagnos*", "Phenotype", "Clinical diagnos*" AND "right heart catheterization (MESH)", "pulmonary catheter", "pulmonar* arter* cathet*", "right heart catheter", "right heart catheter*", "right cardiac* cathet*", "Cardiac* cathet*" AND "exercise" (MESH). For the analysis of mPAP we used the following additional MESH: „mean pulmonary arterial pressure (MESH)", „Pulmonary Arterial Pressure", „mPAP", „meanPAP", „mean pulmonary arterial pressure", „mean pulmonary artery pressure", „PAPm", „Pulmonary Artery Pressure", "Pulmonary Hypertension (MESH)", „Pulmonary Artery Hypertension", „Pulmonary Arterial Hypertension". For the PAWP analysis we used: „pulmonary arterial wedge pressure (MESH)", „pulmonary wedge pressure", „pulmonary artery wedge pressure", „PAWP", „Pulmonary Capillary Wedge Pressure", „pulmonary capillary pressure", „pulmonary artery occlusion pressure", „PAOP", „PCWP", „pulmonary arterial occlusion pressure", „pulmonary venous wedge pressure", „PVWP", „pulmonary venous pressure", „lung venous pressure" AND "Pulmonary Hypertension (MESH)", "Pulmonary Artery Hypertension", "Pulmonary Arterial Hypertension". For PVR analysis we used: „pulmonary vascular resistance (MESH)", „total pulmonary resistance", „PVR", „TPR", „total pulmonary vascular resistance" AND "Pulmonary Hypertension (MESH)", "Pulmonary Artery Hypertension", "Pulmonary Arterial Hypertension".

Excluded studies

Exclusion reason	**Study**
Endpoint other than diagnosis/differential diagnosis	[14,57,58,60,61,64,65,73,75,82,84,85,99,100,129,138-148]
Editorial	[59]
No exercise RHC performed	[56,127,149,150]

Statistical analysis

Diagnostic studies are provided descriptively in the main document.

Figure S3: Flow-Chart for diagnostic studies

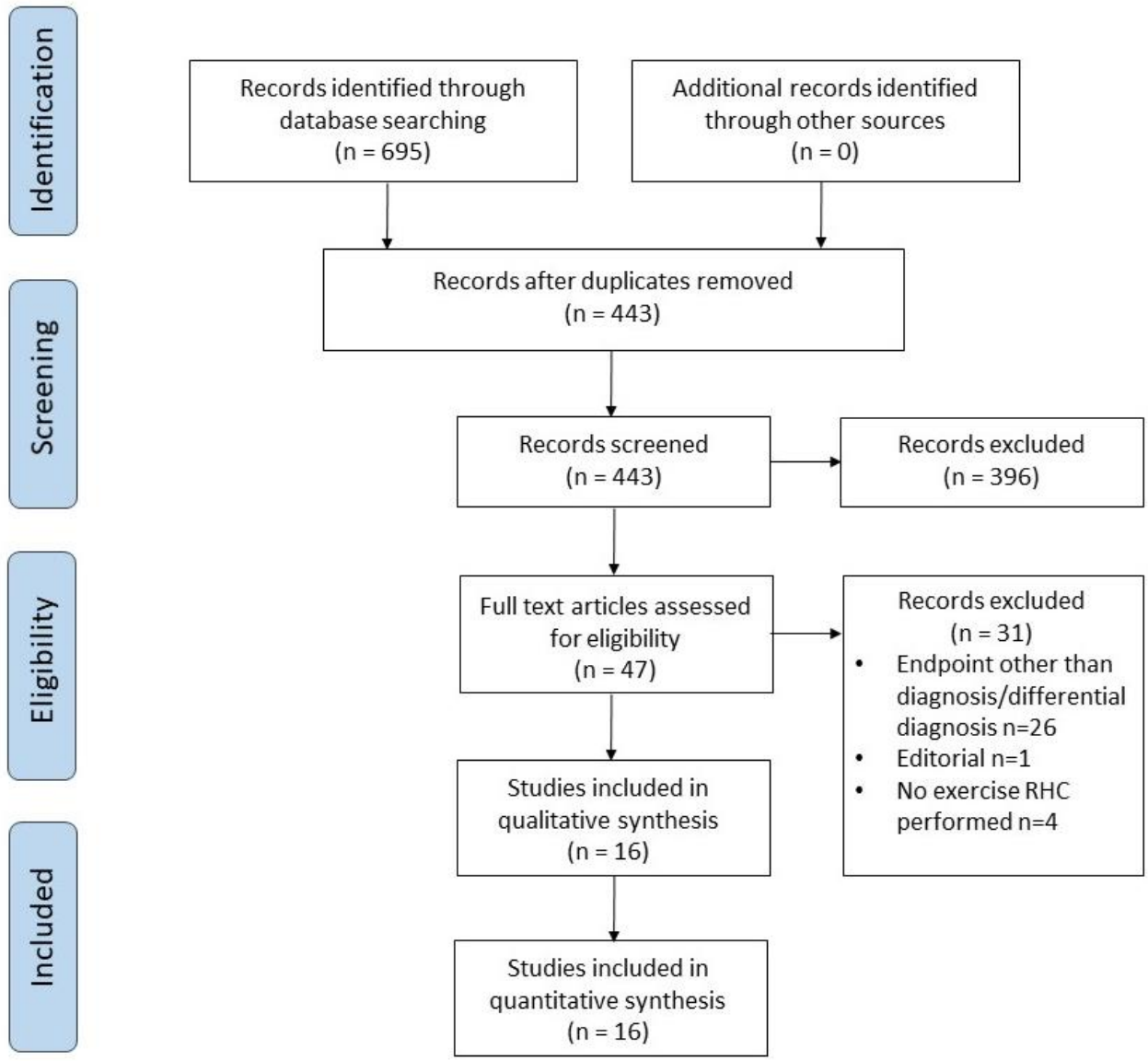


Table S1a: Overview of the included studies for normal data and main characteristics in healthy subjects.

	Publication	N	Age ± SD (range; yrs)	Body position during exercise	Exercise level	Resting mPAP (mmHg)	Exercise mPAP (mmHg)	Restig PAWP (mmHg)	Exercise PAWP (mmHg)	Resting PVR/PVRI (WU)	Exercise PVR/PVRI (WU)	Resting CO (L/min)	Exercise CO (L/min)	Resting CI (L/min/m²)	Exercise CI (L/min/m²)	Resting heart rate (bpm)	Exercise heart rate (bpm)	Watt
1	Andersen et al 2019	16	31 (18-40)	Semi-SUP**	Individual peak	12±3	23±5	8±2	13±4	0.7±0.3	0.6±0.1	5.5±1.1	18.8±1.7	2.9±0.4	10±0.8	62±13	145±17	-
	Andersen et al 2019	15	49 (40-59)	Semi-SUP**	Individual peak	14±3	31±12	9±3	19±10	0.9±0.3	0.7±0.4	5.1±0.9	17.1±2.6	2.7±0.3	9.1±1.3	66±9	138±14	-
	Andersen et al 2019	19	69 (60-80)	Semi-SUP**	Individual peak	14±3	36±7	8±3	23±5	1.3±0.5	0.9±0.3	5±1	14.7±2.8	2.6±0.4	7.9±1.3	63±8	129±16	-
2	Claeys et al 2019	13	46±10	SUP	Individual peak	11.8±2.9	26.6±10.2	-	-	-	-	-	-	3.3±0.9	8.4±2.8	67±12	145±15	-
3	Esfandiari et al 2017	18	58±6	semi-UP	Moderate and light exercise levels	18±2	26±6	12±2	15±5	1.49±0.61	1.2±0.3	4.6±0.6	10.3±1.5	2.5±0.4	5.4±1.8	64±8	122±3	-
	Esfandiari et al 2017	18	54±7	semi-UP	Moderate and light exercise levels	17±3	25±6	11±3	15±5	1.3±0.4	1.14±0.4	5.1±0.9	12.3±3.2	2.8±0.6	6.6±1.9	62±7	121±2	-
4	Wolsk et al 2017	20	29 (20-39)	SUP	Individual peak,moderate and light exercise	13 (95%CI 12-14)	25 (95%CI22-28)	9 (95%CI 8-9)	13 (95%CI10-15)	0.8 (IQR 0.7-1)	0.7 (95%CI 0.6-0.8)	-	-	2.9 (95%CI 2.6-3.1)	9.9 (95%CI 9.6-10.4)	63 (95%CI 57-69)	141 (95%CI 132-151)	174 (95%CI 155-192)
	Wolsk et al 2017	22	49 (40-59)	SUP	Individual peak, moderate and light exercise	15 (95%CI 13-16)	32 (95%CI27-38)	9 (95%CI 8-10)	19 (95%CI15-23)	1 (IQR 0.8-1.2)	0.8 (95%CI 0.8-1)	-	-	2.8 (95%CI 2.6-2.9)	8.8 (95%CI 8.4-9.3)	64 (95%CI 60-69)	126 (95%CI 117-135)	144 (95%CI 129-159)
	Wolsk et al 2017	20	69 (60-80)	SUP	Peak, moderate and light exercise level	15 (95%CI 14-16)	39 (95%CI36-43)	8 (95%CI 7-9)	23 (95%CI21-25)	1.5 (IQR 1.2-1.7)	1.1 (95%CI 0.9-1.4)	-	-	2.6 (95%CI 2.4-2.8)	7.9 (95%CI 7.2-8.6)	62 (95%CI 58-66)	128 (95%CI 121-136)	130 (95%CI 113-147)
5	Wright et al 2016	28	55±6	semi-UP	Moderate and light exercise levels	17±3	25±6	11±3	15±5	1.28±0.39	0.96±0.38	4.8±0.8	11.1±2.8	-	6.8±1.5	63±8	122±2	-
6	Claessen et al 2015	14	36±15	SUP	Individual peak	10±3	22±8	-	-	-	-	6.2±1.9	16.2±5.3	3.3±0.8	8.5±2.3	66±7	149±11	-
7	van Empel et al 2014	12	54±2	SUP	Individual peak	13±1	29±2	8±1	16±2	-	-	-	-	2.9±0.2	7.2±0.3	60±3	118±5	114±12
8	Andersen et al 2012	10	46±5	SUP	Individual peak	15±4	28±8	9±2	16±6	PVRI 2.01±1.2	PVRI: 1.3±0.3	-	-	3±0.3	9.4±1.6	64±8	129±23	-
9	Maeder et al 2010	8	61±12	SUP	Individual peak	16±4	32±8	10±4	20±7	PVRI 1.9±0.8	PVRI: 1.5±0.7	-	-	3.5±1	7.4±1.4	72±25	112±20	-
10	Regenstein er et al 2009	10	39±6	UP	Individual peak	16.6±3	30.3±6.7	8±2.2	16.7±3.7	-	-	-	13.5±2.1	2.4±0.3	7.6±1.1	84±11	166±15	123±27.5
11	Lonsdorfer-Wolf et al 2003	7	38±5	UP**	Peak, moderate and light exercise level	13.5±2	26.5±5.6	-	-	-	-	5.4±1.5	20±3.3	-	-	79±10	178±8	276±50

Data is presented as mean ± standard deviation (SD) or median (IQR), unless otherwise stated. 95%CI: 95% confidence interval; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; CO: cardiac output; CI: cardiac index; HR: heart rate; yrs: years; WU: wood units; L: liter; min: minute; bpm: beats per minute; UP: upright; SUP: supine; semi-UP: semi-upright; semi-SUP: semi-supine. Exercise protocol was ergometry for all studies. ** body position is different at rest

Table S1b: Overview of the included studies for normal data and main characteristics in healthy patients (subjects claimed to be healthy by the authors presenting with dyspnea on effort but having normal pulmonary hemodynamics and normal clinical work-up).

	Publication	N	Age ± SD (yrs)	Body position during exercise	Exercise level	Resting mPAP (mmHg)	Exercise mPAP (mmHg)	Restig PAWP (mmHg)	Exercise PAWP (mmHg)	Resting PVR/PVRI (WU)	Exercise PVR/PVRI (WU)	Resting CO (L/min)	Exercise CO (L/min)	Resting CI (L/min/m^2)	Exercise CI (L/min/m^2)	Resting heart rate (bpm)	Exercise heart rate (bpm)	Watt
1	Singh et al 2020 [151]	24	50±14	UP**	Individual peak	14±3	27±5	6±2	12±5	1.7±0.6	1.36±0.61	5.1±2.1	12.9±5.3	-	-	82±15	144±33	142±81
2	Jain et al 2019 [152]	23	50.7±18	SUP	Moderate exercise level	15.6±4.2	21.8±7.8	7.7±2.8	10.8±4.7	1.4±0.6	1.02±0.44		-	3.3±0.6	5.8±1.2	-	-	-
3	Watts et al 2018 [153]	39	32±6	SUP	Light exercise level	13.8±2.8	20.1±4.4	7.9±2.4	9.4±3	0.9±0.5	0.83±0.31	-	-	3.5±0.7	-	69±12	109±14	-
4	Oliveira et al 2016 [154]	41	61 (>50)	UP	Individual peak	12±3	23±5	4±3	9±4	1.68±0.57	1.2±0.45	5 (IQR 3.8-5.8)	12.1 (IQR 9.4-14.2)	2.6 (IQR 2.2-3.1)	6.6 (IQR 5.9-7.9)	-	143±19	103 (IQR 87-140)
	Oliveira et al 2016	25	44 (<50)	UP	Individual peak	12±4	22±4	4±3	9±5	1.31±0.53	0.82±0.26	5.9 (IQR 4.6-7.8)	16.2 (IQR 13.8-19.2)	3.2 (IQR 2.7-3.7)	8.6 (IQR 8-10.3)	-	163±18	148 (IQR 133-173)
5	Held et al 2016 [155]	41	63±13	SUP	Individual peak	15 (IQR 2)	28 (IQR 16.3)	7 (IQR 3.5)	11 (IQR 9.5)	1.65 (IQR 1.5125)	-	5.2 (IQR 1.5)	9.3 (IQR 4.5)	2.6 (IQR 0.7)	4.9 (IQR 1.9)	-	-	100
6	Lau et al 2016 [156]	26	51±13	SUP	Individual peak	14±4	25±5	7±3	12±5	1.1±0.6	1±0.4	6.4±2.1	12.8±2.6	-	-	72±14	112±21	58±24
7	van Empel et al 2014 [157]	20	67±8	SUP	Individual peak	15.6±4.1	30.7±6.9	8.7±3	18.1±6.4	1.3±0.6	1.2±0.3	-	-	3.1±0.6	6±1.3	64±11	116±19	-
	van Empel et al 2014	35	40±9	SUP	Individual peak	15.5±3.1	24.4±6.5	9.2±2.6	14±4.4	1.1±0.8	0.9±0.4	-	-	3.3±0.8	6.8±1.1	79±16	132±18	-
8	Lewis et al 2011 [158]	19	60±12	UP	Individual peak	15±1	29±1	6±1	17±1	2.01±0.19	0.8±0.08	5±0.3	15.5±0.8	-	-	72±3	137±4	142±11
9	Bonderman et al 2011 [159]	10	50±10	SUP	Light exercise level	19±6	25±7	11±6	15±7	1.3±0.6	0.89±0.53	7.3±2.7	10.8±4.4	-	-	78±16	104±28	-

Data is presented as mean ± standard deviation (SD) or median (IQR), unless otherwise stated. IQR: interquartile range; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; CO: cardiac output; CI: cardiac index; HR: heart rate; yrs: years; WU: wood units; L: liter; min: minute; bpm: beats per minute; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index; CO: cardiac output; CI: cardiac index; HR: heart rate. UP: upright; SUP: supine.

Exercise protocol was ergometry for all studies. ** body position is different at rest

Table S2
Resting and exercise cardiopulmonary hemodynamics in healthy patients in the a) supine and b) upright positions.

a)

Condition	Parameter (unit)	k	Estimate	SD
Rest	mPAP (mmHg)	7	15.0[b]	1.1
Rest	PAWP (mmHg)	7	8.0 [b]	1.1
Rest	PVR (WU)	7	1.2 [a]	0.2
Rest	CO (L/min)	7	6.2[b]	0.6
Rest	CI (L/min/m^2)	7	3.2 [b]	0.4
Rest	RAP (mmHg)	3	4.6	0.4
Rest	HR (bpm)	5	72[b,c]	6
Rest	TPR (WU)	7	2.4 [a]	0.3
Exercise	mPAP (mmHg)	7	24.8 [a]	3.6
Exercise	PAWP (mmHg)	7	12.7 [c]	3.0
Exercise	PVR (WU)	7	1.0 [a]	0.3
Exercise	CO (L/min)	7	11.8[c]	1.6
Exercise	CI (L/min/m^2)	7	6.2[c]	0.8
Exercise	RAP (mmHg)	1	4.5	0.4
Exercise	HR (bpm)	5	116 [c]	11
Exercise	TPR (WU)	7	2.1 [a]	0.5
	mPAP/CO slope (WU)	7	1.7 [a]	0.8
	PAWP/CO slope (WU)	7	0.8 [a]	0.4
	TPG/CO slope (WU)	7	0.8	0.3

b)

Condition	Parameter (unit)	k	Estimate	SD
Rest	mPAP (mmHg)	3	13.1 [b,c]	1.8
Rest	PAWP (mmHg)	3	4.7[c]	1.2
Rest	PVR (WU)	3	1.7 [b]	0.4
Rest	CO (L/min)	3	5.0 [b]	0.2
Rest	CI (L/min/m^2)	3	2.8 [b]	0.4
Rest	RAP (mmHg)	3	2.4 [b,c]	0.6
Rest	HR (bpm)	1	72 [b]	1
Rest	TPR (WU)	3	2.5 [c]	0.5
Exercise	mPAP (mmHg)	4	25.3	3.3
Exercise	PAWP (mmHg)	4	11.8	3.8
Exercise	PVR (WU)	4	1.0	0.3
Exercise	CO (L/min)	4	14.2	2.1
Exercise	CI (L/min/m^2)	4	7.5	1.1
Exercise	RAP (mmHg)	4	6.8	2.1
Exercise	HR (bpm)	4	147	12

Exercise	TPR (WU)	4	1.8	0.3
	mPAP/CO slope (WU)	3	1.3	0.3
	PAWP/CO slope (WU)	3	0.8	0.3
	TPG/CO slope (WU)	3	0.5	0.3

Note. [a]significant influence of age (or age-dependency); [b] significant difference between rest and exercise conditions; [c]significant difference as compared to healthy participants (Table 1a and 1b); dSAP and sSAP not reported because there was max 1 study per condition

Data are presented as weighted mean ± SD. HR: heart rate; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; RAP: right atrial pressure; TPG: trans-pulmonary gradient; bpm: beats per minute; WU: wood units;

Slopes were only calculated when rest and exercise measurements were performed in the same position.

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