The effect of aerobic exercise training on pulse wave velocity in adults with and without long-term conditions –a systematic review and meta-analysis

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Supplementary material

Methods:

Eligibility criteria

The inclusion criteria: population - any adult population; interventions -supervised aerobic exercise training, for a minimum of 3 weeks; comparator- no control; outcomes- aortic stiffness measured using applantation tonometry, ultrasound measuring artery wall diameter or cardiac MRI; study design - studies with pre and post intervention measurements. Exclusion criteria: no objective measure of aortic stiffness; studies without exercise training as an intervention; abstract only.

Search strategy for the systematic review.

The full search terms for MEDLINE are as follows:

"VASCULAR STIFFNESS"/ OR ((aortic OR vascular OR arterial) ADJ3 stiff*).ti,ab OR "PULSE WAVE ANALYSIS"/ OR (pulse wave velocity).ti,ab))

AND

(exp EXERCISE/ OR exp EXERCISE THERAPY/ OR exp PHYSICAL EXERTION/ OR exp SPORTS/ OR exp EXERCISE MOVEMENT TECHNIQUES/ OR exp LOCOMOTION/ OR exp FITNESS CENTERS/ OR (physical ADJ3 (exertion OR endurance OR therap* OR conditioning OR activit* OR fitness)).ti,ab OR (exercis*).ti,ab OR (fitness ADJ3 (train* OR intervention* OR protocol* OR program* OR therap* OR activit* OR regim* OR centre* OR center*)).ti,ab OR ((training OR conditioning) ADJ3 (circuit OR intervention* OR protocol* OR program* OR activit* OR regim*)).ti,ab OR (walk* OR run* OR treadmill OR aerobic OR swim* OR danc*).ti,ab OR ((endurance OR aerobic OR cardio*) ADJ3 (fitness OR train* OR intervention* OR protoco* OR program* OR therap* OR activit* OR regim*)).ti,ab))

AND

ADULT

Study screening and data extraction

Two reviewers independently screened the titles and abstracts for inclusion against the defined eligibility criteria. The full text of the included articles were then screened by two reviewers against the defined eligibility criteria. Any disagreement was resolved by consensus, with the addition of a third reviewer if necessary.

The extracted information included: (1) the participants' demographics (2) disease/health characteristics; (3) intervention; (4) method of the assessment of aortic stiffness; (5) results; (6) statistical analysis. Any disagreements was resolved by consensus and a third reviewer was consulted when disagreement could not be resolved. If data from selected studies were incomplete, the principal study author was contacted.

Each study was assessed for possible risk of bias using the relative tool depending on the study design. For the randomised controlled trials the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2) was used. As for the non-randomised studies, the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool was applied. The national heart, lung, blood institute quality assessment tool for observational cohort and cross-sectional studies was used for the uncontrolled studies.

Statistical analysis

Baseline demographics were analysed using SPSS.

Mean differences between the measures before and after the intervention measures of arterial stiffness were calculated using the reported means and standard deviations. If different measures of central tendency and distribution were available, means and SD were estimated using p-value or 95% confidence interval, or if not available, estimated from baseline SD using a correlation coefficient of 0.681 (derived from the dataset). A sensitivity analysis was performed with a correlation coefficient of 0.5. These imputations followed the guidelines as set out in the Cochrane handbook for systematic reviews of interventions.

A meta-analysis was conducted using the metafor package in R 4.1.1 (R Foundation for Statistical Computing).

Results

e-Table 1. List of excluded studies

Study	Reason for exclusion
Acar, 2014 [1]	No measure of PWV
Acar, 2015 [2]	No measure of PWV
Akawaza, 2013 [3]	No measure of PWV
Akerman, 2019 [4]	Intervention was 2 weeks
Aldabayan, 2017 [5]	Systematic review
Aldabayan, 2019 [6]	Not aerobic exercise
Brozic, 2017 [7]	Unsupervised exercise training
Dobrosielski, 2012[8]	Not aerobic exercise
Eluterio-silva, 2013 [9]	No measure of PWV
Figueroa, 2014 [10]	Not aerobic exercise
Figueroa, 2011 [11]	Not aerobic exercise
Fujie, 2014 [12]	No measure of PWV
Fukuie, 2018 [13]	Not aerobic exercise
Gale, 2011 [14]	Not aerobic exercise
Greenwood, 2015 [15]	Not aerobic exercise
Harris, 2014 [16]	Not aerobic exercise
Howden, 2013 [17]	Exercise and lifestyle
Hraiech, 2016 [18]	Lack of intervention information
Kawamoto, 2014 [19]	No measure of PWV
Kawasaki, 2011 [20]	Unsupervised exercise training
Kim, 2017 [21]	Unsupervised exercise training
Koh, 2009 [22]	Protocol paper
Kurose, 2014 [23]	Not aerobic exercise
Lee, 2015 [24]	Not aerobic exercise
Mcneilly, 2012 [25]	Unsupervised exercise training
Michishita, 2017 [26]	Exercise and lifestyle
Mihaescu, 2013 [27]	Not aerobic exercise
Miura, 2015 [28]	Not aerobic exercise
Moore, 2017 [29]	Not aerobic exercise
Murakami, 2005 [30]	Lack of intervention information
Mustata, 2004 [31]	No measure of PWV
O'Connor, 2017 [32]	Duplicate data
Okamoto, 2019 [33]	Unsupervised exercise training
Pagonas, 2017 [34]	Unsupervised exercise training
Patil, 2015 [35]	Not aerobic exercise
Pierce, 2016 [36]	Unsupervised exercise training
Ramirez, 2019 [37]	Duplicate data
Son, 2016 [38]	Not aerobic exercise
Streese, 2018 [39]	Protocol paper
Tanaka, 2013 [40]	No measure of PWV
Tabara, 2007 [41]	No measure of PWV
Totosy, 2015 [42]	Not aerobic exercise
Trzos, 2007 [43]	No intervention

Vanfleteren, 2014 [44]	Not aerobic exercise
Yuan, 2016 [45]	No measure of PWV

e-Table 2. Description of the uncontrolled trials included in this review.

Uncontrolled trials							
Study	**Country**	**Participant's characteristics**	**N**	**Age (years)**	**Sex at birth (% male)**	**BMI (kg/m^2)**	**Type of PWV measured**
Alkatan et al, 2016 [46]	USA	Osteoarthritis	24	61 [5]	8	31.6 [8.3]	cfPWV
Alkatan et al, 2016 [46]	USA	Osteoarthritis	24	59 [5]	8	33.9 [8.3]	cfPWV
Bellia et al, 2017 [47]	Italy	Early onset of type II diabetes	11	59 [8]	82	27.7 [2.8]	rPWV
Chacaroun et al, 2020 [48]	France	Obesity	11	56 [11]	73	31.8 [3.2]	cfPWV
Clark et al, 2020 [49]	Australia	Overweight or obese	16	30 [6]	100	29.0 [3.1]	cfPWV
Clark et al, 2020 [49]	Australia	Overweight or obese	12	26 [8]	100	28.2 [2.5]	cfPWV
Cocks et al, 2013 [50]	UK	Healthy	8	21 [3]	100	22.6 [4.5]	cfPWV
Collier et al, 2008 [51]	USA	Prehypertension or stage 1 hypertension	15	50 [2]	67	29.4 [1.8]	cfPWV
Collier et al, 2011 [52]	USA	Pre-hypertension to stage 1 hypertension	10	46 [5]	100		cfPWV
Collier et al, 2011 [52]	USA	Pre-hypertension to stage 1 hypertension	10	54 [5]	0		cfPWV
Collier et al, 2015 [53]	USA	Obese pre- and stage1 hypertensive	10	54 [9]	70	33.5 [4.4]	cfPWV

Fantin et al, 2012 [54]	Italy	Healthy	10	67 [6]	0	29.5 [5.2]	cfPWV
Fantin et al, 2012 [54]	Italy	Hypertension	11	70 [5]	0	28.2 [3.1]	cfPWV
Fernandes et al, 2020 [55]	Brazil	Parkinson's Disease	12	68 [9]	62	25.5 [4.7]	PWV
Fernandes et al, 2020 [55]	Brazil	Parkinson's Disease	9	70 [8]	58	26.8 [4.1]	PWV
Gainey et al, 2016 [56]	Thailand	Type II diabetes	18	63 [9]	18	26.6 [5.9]	baPWV
Gainey et al, 2016 [56]	Thailand	Type II diabetes	11	58 [10]	20	27.1 [4.6]	baPWV
Gelinas et al, 2017 [57]	Canada	COPD	24	69 [7]	54	27.8 [2.8]	cfPWV
Gelinas et al, 2017 [57]	Canada	Healthy	20	64 [5]	50	26.2 [3.0]	cfPWV
Hansenn et al, 2018 [58]	Switzerland	Unipolar depression	19	38 [12]	26	22.6 [3.3]	cfPWV
Hansenn et al, 2018 [58]	Switzerland	Unipolar depression	11	38 [10]	27	24.9 [5.2]	cfPWV
Hayashi et al, 2005 [59]	Japan	Healthy	17	50 [3]	100		cfPWV
Jamka et al, 2021 [60]	Poland	Abdominal obesity	52	55 [7]	0	34.5 [4.5]	cfPWV
Kakiyama et al, 2005 [61]	Japan	Healthy	10	21 [3]	100	21.0 [4.9]	aPWV
Laskey et al, 2013 [62]	USA	Stable coronary heart disease	15	61 [11]	54		cfPWV
Lane et al, 2014 [63]	USA	Healthy	25	24 [1]	0	25.0 [4.0]	cfPWV
Lane et al, 2014 [63]	USA	Healthy	28	24 [1]	100	25.0 [3.0]	cfPWV

Lee et al, 2018 [64]	Korea	Subacute stroke	19	58 [14]	47	25.2 [3.1]	baPWV
Lee et al, 2018 [64]	Korea	Subacute stroke	18	64 [11]	56	24.5 [2.1]	baPWV
Li et al, 2012 [65]	China	Type II diabetes	27	52 [1[	56	25.9 [3.1]	cfPWV
Li et al, 2012 [65]	China	Type II diabetes	28	50 [7]	54	26.1 [3.7]	cfPWV
Nishiwaki et al, 2011[66]	Japan	Healthy	8	56 [3]	0		baPWV
Olver et al, 2016 [67]	USA	Healthy	8	23 [6]	100		PWV
Park et al, 2020 [68]	Japan	Obese and overweight	21	49 [9]	100	27.7 [2.3]	baPWV
Park et al, 2020 [69]	USA	Peripheral artery disease	25	60 [10]	0	22.5 [2.4]	baPWV
Rakobowchuk et al, 2013 [70]	UK	Healthy	9	24 [3]	0	24.4 [2.2]	baPWV
Rakobowchuk et al, 2013 [70]	UK	Healthy	11	23 [2.5]	0	22.7 [3.1]	baPWV
Ramírez-Vélez et al, 2018 [71]	Colombia	Healthy	11	32 [8]	40	25.5 [4.2]	aPWV
Ramírez-Vélez et al, 2018 [71]	Colombia	Healthy	9	31 [6]	56	23.6 [3.6]	aPWV
Ranadive et al, 2016 [72]	USA	Healthy	36	24 [5]	50	24.7 [3.7]	cfPWV
Ranadive et al, 2016 [72]	USA	Healthy	26	24 [4]	39	29.4 [6.6]	cfPWV
Sabatier et al, 2008 [73]	USA	Healthy	13	33 [5]	0	29.1 [9.1]	PWV
Sauvet et al, 2017 [74]	France	Healthy	16	27 [5]	100	23.6 [0.6]	PWV

Scott et al, 2019 [75]	UK	Type I diabetes	7	29 [13]	71	29.2 [3.2]	cfPWV
Scott et al, 2019 [75]	UK	Type I diabetes	7	29 [8]	71	25.3 [3.2]	cfPWV
Shi et al, 2014 [76]	Japan	Healthy	14	27 [10]	100	23.1 [3.7]	baPWV
Slivovskaja et al, 2017 [77]	Lithuania	Metabolic syndrome	57	53 [7]	46	30.6 [3.7]	cfPWV
Suntraluck et al, 2016 [78]	Thailand	Type II diabetes	14			26.8 [4.5]	baPWV
Suntraluck et al, 2016 [78]	Thailand	Type II diabetes	15			26.0 [3.5]	baPWV
Szucs et al, 2018 [79]	Hungary	COPD	40	65 [7]	53	28.0 [7.0]	PWV
Vogel et al, 2013 [80]	France	Healthy	71	66 [7]	51	27.4 [3.4]	cfPWV
Way et al, 2020 [81]	Australia	Type II diabetes	12	55 [2]	50	34.3 [3.7]	cfPWV
Way et al, 2020 [81]	Australia	Type II diabetes	12	57 [2]	58	37.5 [5.4]	cfPWV

Data are expressed as mean [SD] unless specified. Abbreviations: aPWV, aortic pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; baPWV, brachial-ankle pulse wave velocity; rPWV, radial pulse wave velocity

Training programme of the controlled studies

e-Table 3. Details of the training programmes of the controlled studies of this review. The intensity of the programme is defined in table 4.

Randomised controlled trials						
Study	**Duration of the programme (weeks)**	**Frequency (per week)**	**Intensity**	**Type of exercise**	**Target exercise session (min)**	**Target exercise duration throughout the intervention (min)**
Adams et al, 2017	6	3	3	Walking/running	25	450
Beck et al, 2013	8	3	2	Running	60	1440
Bouaziz et al, 2019	9.5	2	2	Cycling	30	570
Ciolac et al, 2010	16	3	2	Walking/running	40	1920
Deiseroth et al, 2019	12	3	3	Walking	28	1008
Goldberg et al, 2012	4	3	3	Cycling	30	360
Graham-Brown et al, 2021	24	3	3	Cycling	30	2160
Greenwood et al, 2015	12	3	3	Cycling/running	60	2160
Ha et al, 2018	12	3	4	Other	40	1440
Hasegawa et al, 2018	8	3	2	Cycling	40	1080
Hasegawa et al, 2018	8	3	2	Cycling	45	1080
Hannemann et al, 2020	12		3	Cycling	35	420
Hanssen et al, 2017	12	2	3	Running	45	1080
Headley et al, 2014	16	3	2	Unclear	45	2160
Heydari et al, 2013	12	3	3	Cycling	20	720

Ho et al, 2020	8	3	0	Cycling	20	480
Kang et al, 2016	12	5	1	Walking	40	2400
Kim et al, 2017	8	4	3	Cycling	30	900
Koh et al, 2010	24	3	4	Cycling	30	2160
Madden et al, 2013	24	3	3	Cycling/running	40	2880
Madden et al, 2009	12	3	3	Cycling/running	40	1440
Mora-Rodriguez et al, 2018	24	3	3	Cycling	40	3240
Nualnim et al, 2012	12	4	2	Swimming	40	1920
Oliveira et al, 2015	8	3	2	Cycling/running	30	720
Oudesgeest-Sander et al, 2013	52	3	3	Cycling	30	4680
Pascoalino et al, 2015	12	3	3	Walking/running	40	1440
Silva et al, 2019	16	3	2	Cycling	30	1440
Suguwara et al, 2012	8	3	1	Cycling	40	960
Yoshizawa et al, 2009	12	2	2	Cycling	30	720
Zempo-Miyaki	8	3	2	Cycling	45	1080
Non-randomised controlled trials						
Study	**Duration of the programme (weeks)**	**Frequency (per week)**	**Intensity**	**Type of exercise**	**Target exercise session (min)**	**Target exercise duration throughout the intervention (min)**
Bahmanbeglou et al,	8	3	3	Running	30	744
Donley et al, 2014	8	3	3	Cycling	60	1440
Donley et al, 2014	8	3	3	Cycling	60	1440
Fujie et al, 2020	8	3	2	Cycling	45	1080
Fujie et al, 2020	8	3	2	Cycling	45	1080

Holloway et al, 2018	6	3	3	Cycling	50	170
Kim et al, 2018	16	2	2	Other	40	1280
Mamen et al, 2020	8	3	2	Other	17	408
Shenouda et al, 2017	12	3	2	Cycling	45	1620
Soriano et al, 2017	12	2	2	Running	75	1800
Wong et al, 2018	12	4	4	Other		
Vivodtzev et al, 2010	4	5	3	Cycling	30	600
Cross-over trials						
Study	**Duration of the programme (weeks)**	**Frequency (per week)**	**Intensity**	**Type of exercise**	**Target exercise session (min)**	**Target exercise duration throughout the intervention (min)**
Ferrier et al, 2001	8	3	2	Cycling	30	720
Toussaint et al, 2008	12	3	0	Cycling	30	1080

Classification of the exercise prescription

e-Table 4. Classifying intensity for exercise prescription

	Low intensity (1)	Moderate intensity (2)	High intensity (3)	Very high intensity (4)	Guideline
Borg	<3	3	4-6	>6	ATS/ERS[3]/ACSM[4]
W_{peak}	<40%	40-59%	60-79%	≥80%	ACSM for COPD
Walking speed (%max)	<40%	40-59%	60-79%	≥80%	ACSM for COPD
Walking speed from 6MWT	<80%	-	>80%	-	Australian PR guidelines[5]
%max Heart rate	<64%	64-76%	77-95%	≥96%	ACSM guidelines for healthy adults
% heart rate reserve	<40%	40-59%	60-89%	≥90%	ACSM guidelines for healthy adults
% age predicted max heart rate	<64%	64-76%	77-95%	≥96%	No guidelines, based on ACSM HR guidelines
$\%\dot{V}O_{2peak}$	<45%	46-63%	64-90%	≥91%	ACSM guidelines for healthy adults
At anaerobic threshold			all		
Self-selected intensity	All				

Meta-analysis of measures of PWV

e-Table 5. Meta-analysis and meta-regression of measurement method of PWV in controlled studies

Variable	Meta-analysis of each PWV method for controlled studies			Meta-regression controlled age, sex at birth and baseline cfPWV		
	Number of studies	Estimate (95% CI)	P-value	Number of studies	Estimate (95% CI)	P-value
cfPWV	35	-0.65 (-0.89 to -0.42)	<.0001*	35	-0.006 (-0.05 to 0.04)	0.81
aPWV	4	-0.74 (-1.15 to 0.32)	0.16	4	-0.02 (-0.37 to 0.34)	0.11
baPWV	4	-0.74 (-1.15 to -0.32)	0.0005*	4	0.23 (-0.16 to 0.61)	0.15
cbPWV	3	-0.97 (-1.62 to -0.32)	0.004*	3	-0.44 (-1.04 to 0.16)	0.15
PWV unspecified	2	-0.07 (-0.34 to -0.20)	0.60	2	0.40 (0.02 to 0.78)	0.04*
rPWV				1	-1.64 (-2.74 to -0.54)	0.004*

cfPWV, carotid-femoral pulse wave velocity; aPWV, aortic pulse wave velocity; baPWV, brachial-ankle pulse wave velocity; cbPWV, carotid-brachial pulse wave velocity; PWV, pulse wave velocity; rPWV, radial pulse wave velocity.

e-Table 6. Meta-analysis of equipment used to measure PWV

Equipment	Meta-analysis of equipment used to measure PWV		
	N=	Estimate (95% CI)	P-value
Applantation tonometry	26	-0.73 (-1.00 to -0.45)	0.15
Endervis -Vascular Explorer	3	-0.28 (-1.78 to 1.21)	0.71
Volume plethysmographic device	3	-0.80 (-1.43 to -0.17)	0.13
Pulsepen device	3	-0.63 (-1.31 to 0.05)	0.06
Doppler probes	4	-1.09 (-2.38 to 0.20)	0.10
Complior SP device	6	-0.67 (-1.23 to -0.11)	0.08
Oscillometric monitor	3	-0.008 (-0.17 to 0.16)	0.92
Automatic wave form analyser	3	-1.04 (-2.65 to 0.57)	0.21
Semiautomated device	4	-1.19 (-2.63 to 0.25)	0.11
24h PWA monitor	5	-0.07 (-0.38 to 0.24)	0.66
SphygmoCor XCEL®	4	-0.04 (-0.40 to 0.32)	0.82
BPLab® ambulatory blood pressure monitoring system	3	-0.30 (-1.37 to 0.77)	0.58
TU-100 and VP-2000	2	-0.25 (-0.78 to 0.28)	0.35
Cardiac magnetic resonance imaging	2	-1.70 (-2.96 to -0.44)	0.83

Diagnostics of the main meta-analysis

Q-Q plots were created to check normality for each meta-analysis and meta-regression model. For the meta-analysis of RCTs, the model was repeated fit leaving out one study at a time to detect any undue influence of a single study. The effect remained significant in each of these conditions.

Sensitivity analyses

Multiple sensitivity analyses were performed.

1. Method of imputing change standard deviation (SD); studies were classified according to the method of imputing change SD using the guidelines stated in the Cochrane handbook for systematic reviews [82]:
    a. No imputation, the raw values were used
    b. Change SD estimated from presented test statistic (p value, t value or 95% confidence interval)
    c. Imputed based on baseline SD and computed correlation coefficient of 0.681. A sensitivity analysis was also run with a correlation coefficient of 0.5 (as recommended by the Cochrane handbook)
2. Excluding the three studies that had a significant influence on the results [83-85], the difference between these results and the main meta-analysis was not significant (p=0.32)
3. Method of measure of PWV
4. Short versus long duration studies
5. Technique (equipment) used to measure PWV
6. Low risk of bias and blinding outcome assessors

Bubble plots

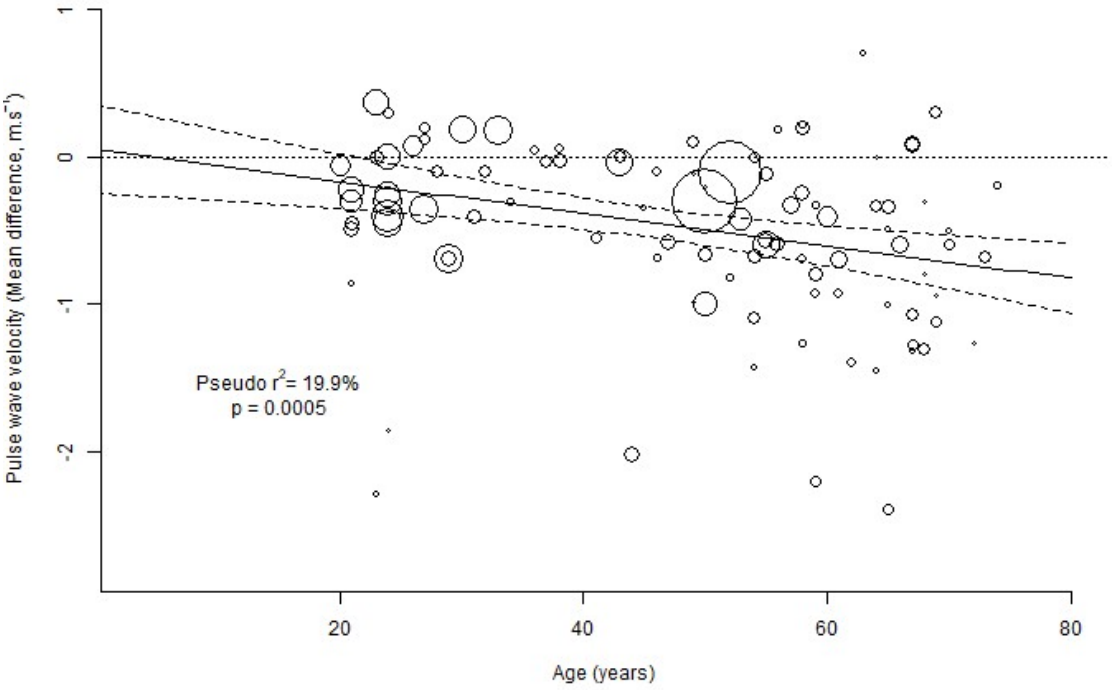

Figure 1. Bubble plot of age vs change in pulse wave velocity.
The size of each bubble is proportional to the weight assigned to that study. The solid line represents the regression line and dashed lines represent the upper and lower 95% CIs. Pseudo r^2 represents the proportion of the total variance explained by the included variable.

Funnel plots

Appears that the more successful trials may be more likely to be published which is highlighted by 3 outlier studies (Adams, Graham-Brown and Zempo-Miyaki) –figure a. The Egger's test for the controlled trials reported p=0.134, indicating no evidence of publication bias statistically.

The Egger's test for all of the included studies (figure b) reported p=0.005 showing significant publication bias.

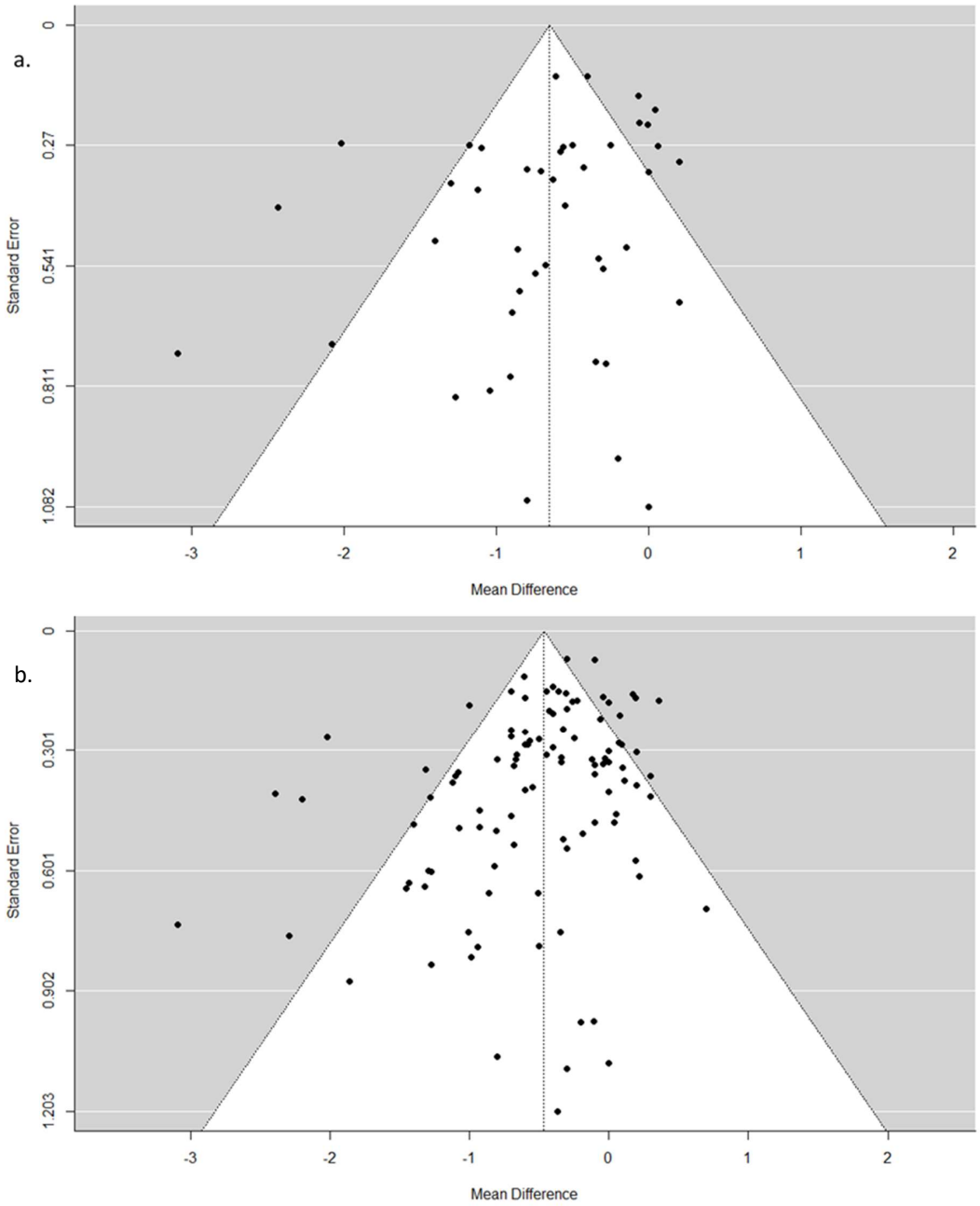

Figure 2. a. Funnel plot of randomised controlled trials. **b.** Funnel plot of all included studies.

If there is no evidence of publication bias, then studies should be evenly distributed on either size of the mean treatment effect line with a similar number of low and high weight studies on either side; a 'bat wing' distribution

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