Exercise and other non-pharmacological strategies to reduce blood pressure in older adults: a systematic review and meta-analysis

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Previous Presentations: Presented at the UK Public Health Science 2017 conference, London, UK November 2017 and published in abstract form

Funding: Philip Herrod is supported by a research training fellowship jointly awarded by the Royal College of Surgeons of England and the Dunhill Medical Trust.

Conflicts of interest: None

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Word Count: 6364
Number of Tables: 2

Number of figures: 8

Number of supplementary digital content files: 7

Abstract

Background: The incidence of hypertension increases with advancing age and represents a significant burden of disease. Lifestyle modification represents the first line intervention in treatment algorithms, however the majority of evidence for this comes from studies involving young participants utilising interventions that may not always be feasible in the elderly.

Methods: This manuscript presents a systematic review of all randomised controlled trials involving participants with a mean age of 65 or over investigating non-pharmacological strategies to reduce blood pressure (BP).

Results: Fifty-three randomised controlled trials were included. The majority of interventions described either aerobic (AET), resistance (RET) or combined exercise training (COM), with limited studies reporting isometric training (IET) or alternative lifestyle strategies. AET, RET, COM and IET all elicited significant reductions in both systolic and diastolic BP, with no additional benefit of COM compared to single modality exercise training.

Conclusion: Three months of traditional exercise-based lifestyle intervention may produce a reduction in BP of approximately 5mmHg systolic and 3mmHg diastolic in older individuals, similar to that expected in younger individuals

Key Words: Blood pressure, hypertension, elderly, non-pharmacological, meta-analysis, systematic review

List of abbreviations

AET	Aerobic exercise training
BP	Blood pressure
CI	Confidence interval
COM	Combined aerobic and dynamic resistance exercise training
DBP	Diastolic blood Pressure
IET	Isometric exercise training
NHS	UK National Health Service
RCT	Randomised controlled trial
RET	Dynamic resistance exercise training
SBP	Systolic blood pressure

Introduction

In the UK, the prevalence of hypertension is estimated at 31% for men and 28% for women; unchanged for a decade [1]. Hypertension increases risk of cardiovascular events and this risk is lowered by reducing blood pressure (BP). A meta-analysis involving 464,000 patients showed both ischaemic heart disease and cerebrovascular events can be significantly reduced by a 10mmHg reduction in systolic blood pressure (SBP) or 5mmHg reduction in diastolic BP (DBP) [2]. Treating hypertension is expensive but is offset by reduction in the need for care following cardio-cerebro-vascular events. Reducing the BP of the population in general may save up to £850 million over 10 years [3–5].

Hypertension is managed pharmacologically for the most part [6–8]. Antihypertensives can be effective in lowering BP [9], but compliance remains an issue as many patients dislike taking medication for asymptomatic disease or experience problematic side effects [10,11][11].

Lifestyle modification is often the first line in management in treatment guidelines [6,7,12,13]. Whilst they are financially attractive [14] and effective within studies [15–27], lifestyle interventions, including sodium intake reduction and various forms of exercise training may suffer from poor compliance outside the setting of randomised controlled trials (RCTs) [28].

There is a well described association between advancing age and hypertension, with prevalence increasing from 8% of men and 2% of women in the 16-24 age range to 66% of men and 78% of women aged 75 and over [1]. However, the majority of studies evaluating lifestyle and exercise interventions have been carried out in younger adults and not the elderly. Clinical guidelines and evidence in older adults is lacking, with a recent systematic review of cardiovascular disease prevention concluding that guidelines are often vague in their coverage of older people and often based on limited evidence [29]. No review to date has evaluated the evidence from lifestyle modification RCTs involving participants with a mean age of 65 or over (the Organisation for Economic Co-operation and Development's definition of elderly [30]), where interventions suitable for younger adults may be difficult for the elderly to adhere to because of mobility impairment and other challenges.[31]. We aim to address this gap in evidence in this review and meta-analysis.

Materials and methods

Study design

This systematic review was registered prospectively with PROSPERO (registration number CRD42017059443) and was carried out in accordance with the PRISMA statement [32]. Only RCTs evaluating a physical activity or lifestyle modification intervention were included. Other inclusion criteria were mean participant age of 65 years or older [30], interventions lasting 2 weeks or more, and trials where resting BP was reported before and after intervention. Trials involving a drug treatment or nutraceutical supplement were excluded.

Literature search

Literature searches were carried out by a trained Clinical Research Librarian using the following databases: MEDLINE, EMBASE, CINAHL, AMED, and PubMed (all inception to 3rd March 2017). No language or date restriction was applied to the searches. The Cochrane library of systematic reviews was searched for relevant reviews and Clinicaltrials.gov was searched for unpublished studies. Previous systematic reviews of related topics were also searched for relevant studies. References of identified potentially relevant studies were hand-searched for further studies. Finally, all studies citing the identified potentially relevant primary studies were screened for inclusion using Google Scholar. Example search strategies can be found in Appendix 1.

Abstracts were screened by one author (PH) with the aid of Rayyan systematic review software (2016, Qatar Computing Research Institute, Doha, Qatar) [33]. Full text versions of potentially relevant primary studies were then independently screened against the inclusion and exclusion criteria by two authors (PH and BD) and agreement to inclusion reached by consensus.

Data extraction

Study characteristics were extracted by one author (PH) with outcome data independently extracted and verified by two authors (PH and JB). Risk of bias for included studies was assessed using the Cochrane Collaboration tool for assessing risk of bias independently by two authors (PH and BD) with any disagreement resolved by consensus. When BP was only reported in graphical form, data were extracted using the online tool WebPlotDigitizer (Version 3.12, Austin, Texas, USA) [34].

Statistical analysis

To facilitate meta-analysis of change variables when standard deviations of change were not reported, standard deviations were imputed using methods described in the Cochrane handbook [35]. These standard deviations were calculated using a correlation coefficient of change of 0.8 (the mean correlation coefficient of change from those studies which reported a standard deviation of change). Outcomes were aggregated using a random-effects model. Changes in blood pressure (systolic and diastolic) are presented as differences in means with 95% confidence intervals (CI) with mmHg as the units. We regarded changes of 10mmHg in SBP and 5mmHg in DBP as clinically significant [2]. We used the I^2 statistic to quantify statistical heterogeneity, with values above 50% as evidence of statistical heterogeneity. We assessed publication bias qualitatively using Funnel plots and quantitatively using Egger's linear regression test ($p<0.05$). We investigated heterogeneity using a random effects, restricted maximum likelihood meta-regression. Covariates included duration of intervention and whether studies included participants with hypertension (BP 140/90) or not. We report the between-study heterogeneity explained by the model (R^2 analogue) with a corresponding p value. The Knapp Hartung modification was used as the variance estimator. To assess the quality of evidence, the GRADE approach [35] was used with evidence downgraded to moderate, low or very low quality owing to concerns over unexplained heterogeneity, indirectness of evidence, possible publication bias, imprecision in effect estimates and concerns over risk of bias. All calculations were carried out using STATA 14 (StataCorp, Texas USA).

Results

Search results

A total of 719 abstracts were screened for inclusion, 666 from the initial literature search, 32 from the reference lists of other identified studies and 21 from other systematic reviews. No relevant unpublished studies were identified on Clinicaltrials.gov. Of the 719 abstracts screened 639 were excluded as not being relevant, leaving 80 studies for full-text review. Of 80 studies, 27 were excluded leaving 53 studies [36–88] for inclusion in the qualitative/quantitative analysis (Figure 1).

Study characteristics

The characteristics of the included studies are shown in Tables 1 and 2. The earliest study meeting inclusion criteria was published in 1989 and the latest in 2016. All studies were published journal articles. The majority of interventions studied can be broadly categorised into aerobic exercise training (AET), dynamic resistance exercise training (RET) (forms of exercise involving moving external loads through a defined range of motion i.e weight training), combined aerobic and dynamic resistance exercise training (COM) [89] and isometric exercise training (IET) (a form of resistance exercise training during which the muscle being exercised exerts a constant force against a fixed load without changing length). Both studies employing IET in this review used a sustained handgrip contraction around a dynamometer as their intervention. Other studies described yoga, dietary interventions, relaxation therapy, music therapy and traditional Chinese alternative therapies (e.g. cobblestone mat walking).

Risk of bias

All included studies carried a high risk of bias in at least one domain (Figure 2). The majority of studies were at high risk of bias due to the innate difficulties in blinding participants to a physical activity intervention. A large number of studies did not describe their random sequence allocation or allocation concealment in sufficient detail to be judged as low risk of bias, and many did not describe blinding of their outcome assessment. Many studies were at risk of reporting bias and some may have suffered from attrition bias. Finally, nearly half of the studies had groups that had either clinically or statistically significantly different BP values at baseline, thus potentially introducing bias to their results.

Data synthesis

It was judged that there were sufficient studies to perform independent meta-analysis for AET, RET, COM and IET interventions. Four studies were not included in the meta-analyses due to lack of an adequate non-intervention control group.

Aerobic exercise

In all, 26 study groups from 24 trials were analysed, comprising 925 individuals in the intervention groups and 784 control participants. AET provided a weighted mean difference in reduction in SBP of -5.09 (95% CI -7.22 to -2.97) mmHg (Figure 3) compared to control, and a difference in DBP of -2.20 (95% CI -3.08 to -1.31) mmHg (Figure 4). There was evidence of statistical heterogeneity in both analyses (I^2=78% and I^2=61% respectively). On meta-regression analysis, neither duration of intervention (R^2=0%; p=0.47 for SBP and R^2=0%; p=0.75 for DBP (supplementary figures 1 and 2)) nor hypertensive baseline status (R^2=4%; p=0.37 for SBP and R^2=0%; p=0.95 for DBP) could explain the between-study heterogeneity. There was no evidence of publication bias in either analysis (p=0.68 and p=0.41 respectively). The quality of evidence of both outcomes was regarded as low using GRADE criteria (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

Resistance exercise

For RET, 13 study groups from 12 trials were analysed, comprising 263 individuals in the intervention groups and 251 control participants. RET provided a reduction in SBP of -5.46 (95% CI -8.61 to -2.31) mmHg (Figure 5) and a reduction in DBP of -2.02 (95% CI -3.31 to -0.73) mmHg (Figure 6). There was evidence of statistical heterogeneity in both analyses (I^2=71% and I^2=54%, respectively). On meta-regression analysis, neither duration of intervention (R^2=0%; p=0.81 for SBP and R^2=0%; p=0.72 for DBP (supplementary figures 3 and 4)) nor hypertensive baseline status (R^2=0%; p=0.69 for SBP and R^2=23%; p=0.19 for DBP) could explain the between-study heterogeneity. There was evidence of an asymmetrical Funnel plot for the DBP analysis (p=0.004) indicating possible publication bias. The quality of evidence was low using GRADE criteria for SBP (concerns over risk of bias and unexplained heterogeneity) and very low for DBP (concerns over risk of bias, unexplained heterogeneity and possible publication bias).

Combined aerobic and resistance training

For COM study groups from 12 trials were analysed, comprising 615 individuals in the intervention groups and 622 control participants. COM provided a reduction of -5.86 (95% CI -8.27 to -3.45) mmHg (Figure 7) in SBP and -3.51 (95% CI -4.43 to -2.59) mmHg in DBP (Figure 8). There was evidence of statistical heterogeneity in the SBP analysis (I^2=73%). On meta-regression analysis, neither duration of intervention (R^2=0%; p=0.65 for SBP and R^2=35%; p=0.18 for DBP (supplementary figures 5 and 6)) nor hypertensive baseline status (R^2=0%; p=0.65 for SBP and R^2=0%; p=0.37 for DBP) could explain the between-study heterogeneity. There was no evidence of publication bias for either analysis (p=0.81 and p=0.51 respectively). The quality of the evidence was low for SBP (concerns over risk of bias and unexplained heterogeneity) and moderate for DBP (concerns over risk of bias).

Isometric exercise

Two studies assessing IET were analysed including 34 individuals in the intervention groups and 32 control participants. IET provided a reduction of -9.14 (95% CI -10.76 to -7.51) mmHg in SBP and -3.01 (95% CI -3.57 to -2.45) mmHg in DBP. There was no evidence of statistical heterogeneity in either analysis (I^2=0% for both). There were too few studies to assess publication bias. The quality of evidence was moderate for both SBP and DBP (concerns over risk of bias).

Other interventions

Three papers [39,63,85] describe dietary interventions including either sodium restriction or calorie control induced weight loss, however there was too much clinical heterogeneity between the interventions to permit meta-analysis. Two further papers [55,56] described cobblestone mat walking, a traditional Chinese remedy, however these were both conducted by the same author at the same institution and so meta-analysis was not carried out. Yoga (2 studies) [38,69], Tai Chi (1 study) [78], relaxation therapy (2 studies)[45,80] and lifestyle advice sessions (1 study) were judged to be sufficiently different interventions to prevent meaningful meta-analysis. One study described music therapy [77].

The dietary intervention studies based on sodium restriction and calorie controlled weight loss (3 studies) had mixed results, leading to significant reductions in both SBP and DBP in two studies but not in the third (supplementary Table 1).

With regard to the alternative interventions, the two studies investigating cobblestone mat walking reported non-significant and significant reductions in both SBP and DBP, respectively. Conversely, one yoga intervention study reported a significant reduction in SBP but no significant change in DBP, while another reported no significant change in DBP (SBP was not reported). Tai chi did not lead to a significant change in either SBP or DBP. Relaxation therapy, lifestyle advice sessions and music (classical) therapy were all associated with significant reductions in both SBP and DBP (supplementary Table 2).

Discussion

This systematic review has demonstrated that AET, RET or both performed together (COM), undertaken regularly over at least a three month period can lead to reductions of 5-6mmHg in SBP and 2-3.5 mmHg in DBP in individuals aged over 65 years. However, this did not reach our *a priori* threshold for clinical significance (10/5 mmHg) [2]. There was no additional benefit seen in exercise programmes lasting longer than 3 months and similar reductions in BP were seen in trials including both hypertensive and non-hypertensive individuals.

These small reductions in BP are similar to those reported by other reviews which have examined lifestyle interventions in much younger patients [17,25,90] and are similar to those expected from the introduction of one antihypertensive agent at half-standard dose [2]. Thus lifestyle intervention alone cannot be recommended as a sole treatment for hypertension but may serve as a useful adjunct to pharmacotherapy. Of note, these reductions are equivalent to those achieved in some large RCTs investigating antihypertensives (such as the PROGRESS [91] and ADVANCE trials [92]). In the ADVANCE trial this magnitude of reduction was associated with significant reductions in events but this was not seen in the PROGRESS trial. In the setting of patients without hypertension, whose BP is below current treatment thresholds for pharmacotherapy, lifestyle interventions may be useful in further reducing (or possibly preventing increases in) BP.
There did not appear to be any additional benefit in combining AET with RET, suggesting that they may both elicit their change in BP through similar mechanisms [93,94]. Similarly, there appears to be no significant additional benefit in extending the duration of interventions beyond 3 months as there was no interaction between intervention duration and magnitude of effect. However, as no studies reported BP follow up data in the months after intervention cessation, it is unknown whether these benefits persist or if continued intervention is required to maintain the benefit. Considering evidence from studies exploring other aspects of exercise adaptation, it may be that detraining would likely lead to benefits being lost rapidly on cessation of intervention [95,96].

Adherence to the interventions in the included studies varied substantially with dropout rates ranging from 0% to 26% [97]. That some dropout occurred at screening for participants who were physically incapable of participating in the interventions may reflect that some older adults find exercise interventions difficult to engage with and sustain. Further work is required to develop interventions that are accessible to those with mobility impairments and agreeable to the majority of older individuals. It is likely that the majority of subjects in the included studies were highly selected volunteers and they may not be representative of the general population.

It is interesting that some studies in this review were published over 25 years ago with others as recently as 18 months ago whilst there are also studies currently prospectively registered on clinical trials registers. That very simple interventions are still being actively studied in older populations serves to highlight concerns about long term sustainability of some interventions, particularly dietary ones [98], but also the need to treat an ageing population with associated health conditions.

Of note, despite a wide ranging search strategy intended to include all forms of lifestyle modification, this review identified very few randomised controlled trials on interventions that were not exercise based. This is despite lifestyle interventions such as sodium restriction and weight loss being recommended in various guidelines [29].

Although the focus of this review has been on the effect of lifestyle interventions on blood pressure, many of the exercise interventions described may have had other benefits to the participants such as an improvement in functional status [99], which may in fact have benefitted their quality of life more than a reduction in blood pressure ever could.

Isometric exercise has the potential for large reductions in BP of up to 9mmHg SBP. However, this figure is based on very limited evidence from only a small number of participants. Of note, of the two studies investigating IET included in this review, one included 9 patients with hypertension in the intervention group whilst the participants in the other study had a mean starting blood pressure of 122/70 mmHg. Despite several decades of research on IET, with studies on younger participants carried out since 1992 [100], a recent systematic review of all IET was only able to include 11 trials of 302 participants [101], whilst another of only isometric handgrip could only include 7 trials and 157 participants [102]. Despite this dearth of high quality published evidence, products claiming efficacy for treatment of hypertension are available for purchase. Further high quality studies are required to investigate this novel intervention in an older population as it has several advantages over other interventions with potential for use in those with physical mobility limitations and being very short in duration (~15 minutes per session) compared with the majority of AET and RET interventions (often 30 minutes to 1 hour per session) [103]. Specifically, this time-efficiency is likely important for intervention uptake and compliance as "lack of time" is a commonly cited barrier to exercise [104]. It remains unclear why such a simple and non-invasive potential therapy for hypertension has not been studied robustly in the elderly to date.

Limitations

A limitation of this review, as is common to all systematic reviews, is the potential for missed studies from our search. In order to mitigate against this the search was carried out across multiple databases and an attempt to find unpublished studies was made using a clinical trials registry. Furthermore, a detailed hand search of all references of included studies was undertaken, together with another hand search of all articles citing included studies in order to minimize this risk. However, it is not inconceivable that some studies were potentially missed.

Although aiming to review the literature on a population over the age of 65 years, we may have included some patients younger than this as our inclusion criteria stipulated a mean study population age of over 65 and not 65 years as an absolute cut off. This decision was taken for a number of reasons including the paucity of papers stipulating a minimum age of 65 and also the large number of papers which did not specify their lower age limit.

A large number of trials included in this review did not provide standard deviations for changes in BP, necessitating imputation using recognised methods from the Cochrane handbook [35]. This is a common issue in trial reporting and this review has attempted to minimise any inaccuracy this may have brought about by imputing SDs from a correlation coefficient calculated from the studies who did present their change SDs. However if physical activity were to alter the variability in change in BP then these assumptions may prove false.

Many of the meta-analyses in this review included trials with large degrees of statistical heterogeneity. A large part of this heterogeneity is most likely accounted for by the large degree of clinical heterogeneity between described interventions and between populations BP at baseline.

The majority of trials in this review were at high risk of bias in at least one domain, which may exaggerate effect estimates in meta-analyses [105]. Particular concern must be paid to the lack of blinding of BP measurement in the majority of included studies. Furthermore, the majority of these trials relied on the use of office BP (measurements at one time point during one visit to the laboratory) as their primary endpoint, rather than ambulatory BP (which was only measured in 4 studies), which may cast doubt on the ability of the interventions to reduce BP out of the research environment [106,107].

Although the majority of studies included in this review included volunteers of both genders, no study reported changes in BP according to gender. In the context of the known gender differences in BP control, original studies are required to determine whether certain lifestyle interventions may be more effective in each gender [108].

None of the studies described in this review provided any long-term follow up data to demonstrate the on-going benefits to BP after a period of exercise, and further work is required to assess long-term benefits. In addition, it is unclear whether such reductions in BP can be achieved over shorter periods of time, which may have additional clinical relevance, for example for preoperative optimisation in surgical patients [109].

Conclusions

In conclusion, the best available evidence suggests that non-pharmacological lifestyle interventions involving either aerobic exercise training, dynamic resistance exercise training or a combination of the two can lead to statistically significant reductions in both SBP and DBP in older adults. However these reductions failed to reach thresholds for clinical significance and as such cannot be recommended as antihypertensive monotherapy, in the majority of individuals. Further the studies supporting these interventions contain various limitations. Isometric exercise training, with its potential benefits in adherence in the elderly, did show promise, although there is insufficient evidence for its use outside trials in older adults. More studies in the use of IET are required.

Acknowledgements

Philip Herrod is supported by a research training fellowship jointly awarded by the Royal College of Surgeons of England and the Dunhill Medical Trust.
The authors would like to thank the Suzanne Toft, Clinical Librarian at the Royal Derby Hospital for her help with the electronic database searches.

Conflict of interest

No author has a conflict of interest to declare

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Appendix 1

Search strategies were as follows:

MEDLINE

(exp "ARTERIAL PRESSURE"/ OR exp HYPERTENSION/ OR exp "MASKED HYPERTENSION"/ OR exp "WHITE COAT HYPERTENSION"/) NOT exp "HYPERTENSION, PULMONARY"/) AND (exp "LIFE STYLE"/ OR exp "SERVING SIZE"/ OR exp "PORTION SIZE"/ OR exp "DIET, SODIUM-RESTRICTED"/ OR exp "DIET, REDUCING"/ OR exp "DIET, DIABETIC"/ OR exp "DIET, CARBOHYDRATE-RESTRICTED"/ OR exp "DIET, FAT-RESTRICTED"/ OR exp "DIET, MEDITERRANEAN"/ OR exp "DIET, VEGETARIAN"/ OR exp "EXERCISE THERAPY"/ OR exp "WARM-UP EXERCISE"/ OR exp WALKING/ OR exp SWIMMING/ OR exp RUNNING/ OR exp "RESISTANCE TRAINING"/ OR exp "PLYOMETRIC EXERCISE"/ OR exp "PHYSICAL CONDITIONING, HUMAN"/ OR exp "PHYSICAL CONDITIONING, HUMAN"/ OR exp "MUSCLE STRETCHING EXERCISES"/ OR exp "COOL-DOWN EXERCISE"/ OR exp "CIRCUIT-BASED EXERCISE"/ OR exp EXERCISE/ OR exp MUSIC/)) NOT exp "DRUG THERAPY"/) AND (reduc* OR lower).ti,ab) AND exp AGED/) [Document type Meta-analysis OR Multicenter Study OR Randomized Controlled Trial OR Review] [Human age groups Aged] [Humans]"

EMBASE

((((exp "SYSTOLIC BLOOD PRESSURE"/ OR exp "DIASTOLIC BLOOD PRESSURE"/ OR exp "BLOOD PRESSURE VARIABILITY"/ OR exp "BLOOD PRESSURE REGULATION"/ OR exp "BLOOD PRESSURE FLUCTUATION"/ OR exp "ARTERIAL PRESSURE"/) AND (exp "WHITE COAT HYPERTENSION"/ OR exp "SYSTOLIC HYPERTENSION"/ OR exp "RESISTANT

HYPERTENSION"/ OR exp PREHYPERTENSION/ OR exp "METABOLIC SYNDROME X"/ OR exp "MASKED HYPERTENSION"/ OR exp "ESSENTIAL HYPERTENSION"/ OR exp "DIABETIC HYPERTENSION"/ OR exp "BORDERLINE HYPERTENSION"/)) NOT exp "PULMONARY HYPERTENSION"/) AND (exp "LIFESTYLE MODIFICATION"/ OR exp "VEGETARIAN DIET"/ OR exp "MEDITERRANEAN DIET"/ OR exp "LOW CARBOHYDRATE DIET"/ OR exp "LOW CALORY DIET"/ OR exp "HIGH FIBER DIET"/ OR exp PLYOMETRICS/ OR exp "STATIC EXERCISE"/ OR exp "MUSCLE EXERCISE"/ OR exp "LEG EXERCISE"/ OR exp "EXERCISE INTENSITY"/ OR exp "BREATHING EXERCISE"/ OR exp EXERCISE/ OR exp PILATES/ OR exp "DYNAMIC EXERCISE"/ OR exp "CIRCUIT TRAINING"/ OR exp "ARM EXERCISE"/ OR exp "AQUATIC EXERCISE"/ OR exp "ANAEROBIC EXERCISE"/ OR exp "AEROBIC EXERCISE"/ OR exp "MUSIC THERAPY"/ OR exp MUSIC/)) NOT (exp "ANTIHYPERTENSIVE THERAPY"/ OR exp "DRUG THERAPY"/)) AND (reduc* OR lower).ti,ab) AND exp AGED/) [Human age groups Aged 65+ years] [Humans] [Clinical trials Randomized Controlled Trial OR Controlled Clinical Trial OR Multicenter Study]"

CINAHL

((exp "ARTERIAL PRESSURE"/ OR exp "HYPERTENSIVE CRISIS"/ OR exp "HYPERTENSION, ISOLATED SYSTOLIC"/ OR exp "HYPERTENSION, REFRACTORY"/ OR exp "MASKED HYPERTENSION"/ OR exp "HYPERTENSION, WHITE COAT"/) AND (exp "MIND BODY TECHNIQUES"/ OR exp AROMATHERAPY/ OR exp "LIFE STYLE CHANGES"/ OR exp "WEIGHT REDUCTION PROGRAMS"/ OR exp "WEIGHT CONTROL"/ OR exp VEGETARIANISM/ OR exp "MEDITERRANEAN DIET"/ OR exp "DIET, SODIUM-RESTRICTED"/ OR exp "DASH DIET"/ OR exp "DIET, REDUCING"/ OR exp "DIET, LOW CARBOHYDRATE"/ OR exp "DIABETIC DIET"/ OR exp "RESISTANCE TRAINING"/ OR exp EXERCISE/ OR exp "EXERCISE TEST, CARDIOPULMONARY"/ OR exp MUSIC/ OR exp YOGA/ OR exp "TAI CHI"/ OR exp "RELAXATION TECHNIQUES"/ OR exp MEDITATION/ OR exp "MUSIC THERAPY"/ OR exp "DIET THERAPY"/)) NOT exp "DRUG THERAPY"/) AND (reduc* OR lower).ti,ab) AND exp AGED/) [Publication types Meta Analysis OR Randomized Controlled Trial OR Systematic Review] [Human age groups Aged: 65+ years]"

AMED

(exp "BLOOD PRESSURE"/ OR exp HYPERTENSION/ OR exp "WHITE COAT HYPERTENSION"/) AND (exp "LIFE STYLE"/ OR exp "DIET VEGETARIAN"/ OR exp "DIET MEDITERRANEAN"/ OR exp "CALORIC INTAKE"/ OR exp "WEIGHT TRAINING"/ OR exp EXERCISE/ OR exp SPORTS/ OR exp "PHYSICAL FITNESS"/ OR exp "LEISURE ACTIVITIES"/ OR exp MUSIC/ OR exp YOGA/ OR exp "TAI CHI"/ OR exp "LAUGHTER THERAPY"/ OR exp VISUALIZATION/ OR exp RELAXATION/ OR exp HYPNOSIS/ OR exp

BIOFEEDBACK/ OR exp MEDITATION/)) NOT exp "DRUG THERAPY"/) AND (reduc* OR lower).ti,ab) AND exp AGED/) [Publication types Journal Article OR Review]"

PubMed

((("blood pressure" AND"hypertension"[Title/Abstract]) AND (reduc*[Title/Abstract] OR lower[Title/Abstract])) AND (diet[Title/Abstract] OR exercise[Title/Abstract] OR yoga[Title/Abstract] OR meditation[Title/Abstract] OR lifestyle[Title/Abstract])) AND (aged[Title/Abstract] OR elderly[Title/Abstract]) NOT ("drug therapy" OR medication [Title/Abstract])

Table 1 Characteristics of interventions in included studies

1RM, 1-repetition maximum; HRMax, Maximum Heart Rate; VO2Max, Maximum Oxygen Consumption; Wmax, Maximum Power; MVC, Maximum Voluntary Contraction; DLGA, Dihomo-γ-linolenic acid;

Study	Intervention groups	Details of interventions	Frequency of interventions	Duration of intervention	Mean baseline SBP(SD) (mmHg)	Mean baseline DBP(SD) (mmHg)
Applegate 1992	Combined aerobic exercise, diet induced weight loss of 4.5Kg and low sodium diet	30mins slow walking	4x per week	6 months	143(12)	87(2)
	Non intervention controls				145(10)	88(4)
Barone 2009	Combined aerobic and resistance exercise	45mins aerobic exercise at 60-90% Max heart rate and 7 resistance exercises, 2 sets of each of 12-15 reps at 50%1RM	3x per week	6 months	140(8)	77(7)
	Non intervention controls				142(8)	76(9)
Blumenthal 1989	Aerobic exercise	60 mins comprising 10mins warm up, 30 mins cycling, 15mins brisk walking/jogging and 5mins cool down	3x per week	4 months		

	Yoga	60 mins	2x per week			
	Non intervention controls				Not specified	
	Combined aerobic and resistance exercise	90mins broken down into 30 mins aerobic exercise (cycling, treadmill or stair climbing) aiming for 70-85% HRMax, 30 minutes resistance exercise (9 exercises for 1-2 sets at 6-8 reps of 70-85% 1RM)	3x per week	12 months	131(19)	71(8)
	Diet induced weight loss	Various low impact exercises- 40minutes at 65-70% HRmax	NA		135(19)	76(11)
	Combination of Exercise intervention and dietary intervention	as above	3x per week		139(24)	74(10)
Bouchonville 2014	Non intervention controls				133(19)	72(11)
	Moderate intensity aerobic exercise	45 mins walking at 50% Max heart rate increasing to 70%	3x per week	6 months	121(10)	72(8)
Braith 1994	High intensity aerobic exercise	35mins walking uphill at 50 % max heart rate increasing to 85%	3x per week		120(9)	75(7)

	Non intervention controls				121(12)	74(5)
Broman 2006	Deep water running	30mins interval training 3x 10mins with 2mins rest	2x per week	2 months	138(9)	79(8)
	Non intervention controls				144(19	79(9)
Chomiuk 2013	Nordic Walking	30mins Nordic walking	3x per week	6 weeks	135(13)	76(8)
	Non intervention controls				122(13)	71(8)
Cononie 1991	Resistance training	10 exercises	3x per week	6 months	132(16)	78(9)
	Aerobic exercise	20-30minute walk at 50% VO2max increasing to interval training (jogging, brisk walking or uphill walking for 35-45 mins at 75%-85% VO2 Max)	3x per week		139(16)	81(8)
	Non intervention controls				137(16)	
Dimeo 2012	Aerobic exercise	Treadmill walking - interval training to obtain a lactate of 1.5-2.5	3x per week	2-3months	142(16)	78(9)
	Non intervention controls				140(20)	75(11)

Dusek 2008	Relaxation therapy	20 mins daily plus one supervised 60 minute session per week	Daily	2 months* Only first part of study included as protocol afterwards involved medication changes)	146(6)	77(7)
	Lifestyle advice				145(5)	78(8)
Faulkner 2013	Combined aerobic and resistance exercise	30 mins aerobic exercise (cycling and walking) at 50-85% HR Max, 60 mins of resistance exercise	2x per week	2 months	141(15)	83(8)
	Non intervention controls				136(14)	80(9)
Finucane 2010	Aerobic exercise	60mins cycling at between 50-70% Wmax	3x per week	3 months	139(15)	77(9)
	Non intervention controls				134(7)	73(9)

	Resistance training	8 exercises, 2 sets of 10-15 reps	3x per week	3 months	125(8)	81(6)
Gerage 2012	Stretching programme				123(9)	80(6)
	Resistance training	8 exercises, 2 sets of 15 reps	3x per week	3 months	126(14)	81(9)
Goncalves 2014	Stretching programme				137(16)	88(3)
	Aerobic exercise	Walking (increasing from 5 minutes to 25 minutes by 1 minute per week)	2x per week	6 months	145(21)	73(9)
Hamdorf 1999	Non intervention controls				149(23)	78(11)
	Moderate intensity aerobic exercise	Various low impact exercises- 40minutes at 65-70% HRmax	3x per week	10 weeks	146(18)	75(12)
	High intensity aerobic exercise	Various low impact exercises 40 mins at 85-90%HR max	3x per week		148(23)	77(14)
Huang 2006	Stretching programme				133(24)	75(11)
	Aerobic exercise	25- 45 mins treadmill walking and stair climbing progressing from 50%HR Max to 85% HR Max	3x per week	4 months	133(10)	80(7)
Jessup 1998	Non intervention controls				131(9)	80(5)
Kallinen 2002	Aerobic exercise	1hr walking 2x per week and 1hr step aerobics 1x per week	3x per week	18 weeks	174(15)	83(3)

	Resistance training	60 mins	3x per week		184(15)	80(3)
	Non intervention controls				182(15)	84(2)
Lee 2007	Walking (not directly observed)	Commuity walking intervention delivered by a nurse with verbal encouragement to increase walking. Monitored by a pedometer		6 months	152(11)	84(11)
	Non intervention controls				152(11)	81(9)
Li 2003	Cobblestone mat walking	12-25 mins walking on a cobblestone mat	3x per week	2 months	134(10)	82(9)
	Non intervention controls				132(14)	81(9)
Li 2005	Cobblestone mat walking	6-30 mins walking on a cobblestone mat	3x per week	4 months	135(14)	79(11)
	Walking				135(15)	77(9)
Lim 2015	Combined aerobic, resistance and korean traditional dancing	45 mins at 50-70% HR Max	3x per week	3 months	129(13)	81(7)
	Non intervention controls				130(5)	77(4)

Lovell 2009	Resistance training	25 mins 1 exercise (incline squat) 3 sets of 6-10 reps increasing from 50-90% 1RM	3x per week	4 months	150(6)	87(2)
	Non intervention controls				145(8)	79(5)
Madden 2010	Aerobic exercise	60 mins cycling or treadmill increasing from 50%HR Max to 85% HR max	3x per week	3 months	149(6)	83(2)
	Core and strength training				139(4)	86(2)
Millar 2008	Isometric handgrip	4 sets of 2minute isometric contractions, alternating hands, 30-40%MVC	3x per week	2 months	122(3)	70(1)
	Non intervention controls				117(3)	68(2)
Miura 2015 (hypertensives)	Combined aerobic and resistance training	Circuit training 90 mins	2x per week	3 months	150(9)	84(6)
	Non intervention controls				150(9)	84(7)
Miura 2015 (normotensives)	Combined aerobic and resistance training	Circuit training 90 mins	2x per week	3 months	125(12)	72(8)
					127(9)	74(6)

	Non intervention controls					
Mota 2013	Resistance training	40 mins increasing workload up to 80% 1RM	3-4x per week	4 months	135(15)	76(9)
	Non intervention controls				132(17)	74(7)
Nestel 1993	DLGA	1g/day	NA	6 weeks	119(18)	67(9)
	DLGA + low sodium diet	1g/day plus sodium restriction to 70-80mmol/day	NA	6 weeks	122(13)	68(9)
	Safflower oil	1g/day	NA	6 weeks	117(8)	69(9)
	Safflower oil + low sodium diet	1g/day plus sodium restriction to 70-80mmol/day	NA	6 weeks	121(10)	68(10)
Niederseer 2011	Skiing	Mean 3.5 Hrs skiing per day for 29 days over study period	NA	3 Months	123(12)	82(11)
	Non intervention controls				131(13)	82(14)
Nishijima 2007	Combined aerobic and resistance training	60-90 mins including cycling 20-40 mins from 40-70% VO2 peak	2-4x per week	6 months	139(16)	82(10)
	Lifestyle advice				141(18)	83(11)

	Combined aerobic and resistance training	120 mins in total consisting of cycling 10-25 mins between 25% and 60^ HR reserve and 5 resistance exercises	3x per week	25 weeks	143(10)	79(11)
Ohkubo 2001	Lectures				144(10)	81(9)
	Combined aerobic and resistance training	60 mins of light exercise including walking, balance training, dodgeball, stretching and bodyweight resistance training	2x per week	6 months	136(23)	78(12)
Okumiya 1996	Non intervention controls				146(19)	80(10)
	Aerobic exercise	30-36 mins walking interval training to a target lactate concentration of 1.5-2.5	3x per week	2-3months	138(12)	78(9)
Pagonas 2014	Non intervention controls				133(12)	74(6)
	Yoga	60 mins	6x per week	3 months	147(6)	74(5)
	Brisk walking				146(6)	76(6)
Patil 2015						
	Aerobic exercise	40 mins cycling at 70%VO2 peak	3x per week	4 months	129(12)	75(6)
Posner 1992	Group talks				128(10)	75(6)

Puggard 2000	Combined aerobic and resistance training	60 mins walking and various strength exercises to achieve 69%HR Max	1x per week supervised plus between 1-6x per week home solo training)	8 months	161(19)	84(13)
	Non intervention controls				152(25)	77(11)
Simons 2006	Aerobic exercise	Walking	2x per week	4 months	133(12)	68(6)
	Resistance training	6 exercises, 1 set of 10 reps	2x per week		133(13)	70(9)
	Non intervention controls				128(9)	68(8)
Sousa 2013	Aerobic exercise	30 mins walking, jogging dancing or swimming and 10mins bodyweight resistance exercises	3x per week	9 months	149(25)	80(8)
	combined aerobic and resistance training	7 exercises 3 sets of 8-12 reps increasing from 65%1RM to 75%1RM plus 1x per week plus the aerobic intervention 2x per week	1xper week resistance, 2x per week aerobic		149(15)	83(10)
	Non intervention controls				139(16)	81(11)

Stachenfeld 1998	Aerobic exercise	Either trampolining or treadmill walking increasing from 20mins to 50 mins at 60%Max Hr increasing to 75% Max Heart rate	3-4x per week	4-6 months	144(3)	73(6)
	group stretching and yoga				146(5)	75(4)
Sunami 1999	Aerobic exercise	60 mins cycling at 50%VO2 max	2-4x per week	5 months	142(22)	83(11)
	Non intervention controls				145(24)	83(12)
Taylor 2003	Isometric handgrip	4 x 2minute contractions at 30%MVC, alternating hands 1min rest between contractions	3x per week	10 weeks	156(9)	82(9)
	Non intervention controls				152(8)	87(11)
Teng 2007	Music therapy	25 minutes listening to classical music	Daily	1 month	139(17)	61(14)
	Non intervention controls				134(20)	59(8)
Thomas 2005	Thai Chi	60 mins Yang style Thai Chi	3x per week	1 year	142(17)	72(13)

	Resistance training	60 mins for 30 reps of each of 7 exercises	3x per week		142(23)	72(14)
	Non intervention controls				140(20)	71(12)
Valente 2011	Dietary education	30 mins DASH based dietary education, encouragement to exercise for 30mins per day aiming for 10% wt loss	1x per week	10 weeks	135(13)	79(6)
	Dietary education Plus resistance exercise				130(14)	78(6)
Venturelli 2015	Aerobic exercise	60mins treadmill, elliptical and stepper ergometers at 70% maximum exercise capacity	3x per week	3 months	148(26)	88(16)
	Circuit training	60 mins 4 exercises, 60s work at 1 contraction per second)	3x per week		152(30)	90(13)
	relaxation training	60 mins relaxation and meditation	3x per week		149(43)	88(16)
	Non intervention controls				150(26)	89(27)
Vincent 2003	Resistance training (high intensity)	13 exercises 1 set of 8 reps at 80%1RM	3x per week	6 months	133(10)	64(6)

	Resistance training (low intensity)	13 exercises 1 set of 13 reps at 50% 1RM	3x per week		138(17)	61(9)
	Non intervention controls				130(16)	76(10)
Wang 2012	Aerobic exercise	walking (at least 150mins/wk) plus a variety of strength exercises	5x per week	1 year	132(18)	69(11)
	Non intervention controls				133(17)	70(10)
Westhoff 2007	Aerobic exercise	30 -36min Interval training on a treadmill to reach a lactate concentration of 2-3	3x per week	3 months	137(13)	76(7)
	Non intervention controls				135(11)	73(7)
Westhoff 2008	Upper limb cycling	30 mins upper limb cycling in an interval pattern to achieve a lactate of 1.5-2.5	3x per week	3 months	134(20)	73(22)
	Non intervention controls				136(16)	68(12)
Whelton 1998	Sodium restriction	<80mmol sodium per day	NA	3 months		

		diet induced weight loss of at least			127(12)	71(8)
	Weight loss	4.5Kg			129(11)	71(10)
	Sodium restriction and weight loss	Combination of the other two interventions			128(12)	71(9)
	Non intervention controls				128(12)	72(9)
	Aerobic exercise	21-45mins treadmill or cycling at 60-70% HRMax	3x per week	3 months	134(16)	77(7)
	resistance training	8 exercises 1-2 sets of 8-15 reps at 75% 5RM	3x per week		129(23)	75(10)
	Combined aerobic and resistance training	maximum 30mins aerobic exercise and 1 set of each exercises from other group	3x per week		129(14)	77(8)
Wood 2001	Non intervention controls				134(22)	78(7)

	Aerobic exercise	50-60 mins cycling or walking to achieve 60-85% HR Max	5x per week	3 months	136(11)	82(11)
Yassine 2009	Aerobic Exercise + 500kcal restriction				134(12)	81(13)
	Aerobic exercise	60 mins at 40-60% HR Reserve	2x per week	3 months	138(8)	75(8)
Young 1999	Thai chi				142(10)	77(7)

Table 2 Characteristics of participants in included studies

BP, Blood Pressure; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; T2DM, Type 2 Diabetes Mellitus

Study	**N**	**%Male**	**Mean age**	**BP of participants**	**Other participant characteristics**	**Method of Blood pressure measurement**
Applegate 1992	47	45	65	Mild diastolic hypertension (DBP 85-100mmHg)	Overweight (115% ideal body weight)	Rested seated
Barone 2009	101	49	65	Prehypertension or mild hypertension (SBP 130-159 or DBP 80-99)		Rested (position not specified)
Blumenthal 1989	101	50	67	Not specified	free from coronary artery disease	Rested seated
Bouchonville 2014	107	37	70	Not specified	Obese (BMI>30)	Rested supine
Braith 1994	44	Not specified	66	Not specified	Sedentary	Rested seated
Broman 2006	29	0	69	Normotensive		Rested seated
Chomiuk 2013	68	12	71	Not specified		24Hr Ambulatory
Cononie 1991	56	45	72	Hypertensive and normotensive	free from cardiovascular, respiratory disease or diabetes	Rested seated
Dimeo 2012	50	44	65	Hypertensive (BP > 140/90)	Must be on at least 3 antihypertensives	24 Hr ambulatory and rested seated

Dusek 2008	122	45	67	Isolated systolic hypertension (SBP 140-159, DBP <90)	Taking 2 antihypertensives	Rested seated
Faulkner 2013	68	68		Not specified	TIA - diagnosed within 7 days of randomisation	Rested (position not specified)
Finucane 2010	100	56	71	Not specified	Non diabetic and no ischaemic heart disease	Rested seated
Gerage 2012	29	0	66	Normotensive (BP <140/90)	Sedentary	Rested seated
Goncalves 2014	17	0	66	Hypertensive (BP>160/100)	Sedentary	Rested seated
Hamdorf 1999	38	0	83	Not specified	Sedentary	Rested seated
Huang 2006	52	Not specified	84	Not specified	Sedentary	Rested seated
Jessup 1998	21	50	69	Normotensive	Sedentary	Rested seated and 24Hr ambulatory
Kallinen 2002	42	0	76-78	Not specified		Rested seated
Lee 2007	202	58	71	Hypertensive (SBP 140-179)		Rested seated
Li 2003	40	78	73	Not specified	Sedentary	Rested seated
Li 2005	108	32	78	Not specified	Sedentary	Rested seated

Lim 2015	20	0	71	Not specified		Rested seated
Lovell 2009	24	100	74	BP <150/90	free from cardiovascular disease	Rested (position not specified)
Madden 2010	36	58	71	Hypertensive (BP>130/80) or on antihypertensives	Must have T2DM and hyperlipidaemia	Rested (position not specified)
Millar 2008	49	43	66	Normotensive		Rested (position not specified)
Miura 2015 (hypertensives)	106	0	72	Hypertensive (BP140-149/ 90-99)		Rested supine
Miura 2015 (normotensives)	115	0	72	Normotensive (BP<140/90)		Rested supine
Mota 2013	64	0	67	Hypertensive-medicated	Sedentary	Rested seated
Nestel 1993	66	55	66	Normotensive		Rested seated
Niederseer 2011	42	52	67	Not specified		Rested seated
Nishijima 2007	561	44	67	Both normotensive and hypertensive	BMI 24.2- 34.9 plus two or more risk factors for cardiovascular disease	Rested seated
Ohkubo 2001	39	49	67	Both normotensive and hypertensive	SBP >120	not specified

Okumiya 1996	42	43	79	Not specified	no cardiovascular disease	Rested seated
Pagonas 2014	72	43	67	Hypertensive BP> 140/90 or on antihypertensive medication		24Hr Ambulatory - reported as day and night time.
Patil 2015	60	100	69	Isolated systolic hypertension (pulse pressure > 60, SBP <160. DBP <100)	no other cardiovascular risk factors	Rested seated
Posner 1992	247	38	69	BP <165/90	Sedentary	Rested seated
Puggard 2000	55	0	85	Not specified		resting supine
Simons 2006	64	30	84	normotensive	sedentary and not diabetic	Rested seated
Sousa 2013	59	100	69	Not specified	sedentary	Rested seated
Stachenfeld 1998	17	0	72	normotensive	no cardiovascular disease	Rested supine
Sunami 1999	40	50	67	normotensive		not specified
Taylor 2003	17	59	67	Hypertensive (BP>140/85)		Rested seated
Teng 2007	30	27	81	Hypertensive		Rested seated
Thomas 2005	207	55	69	Normotensive		Rested seated

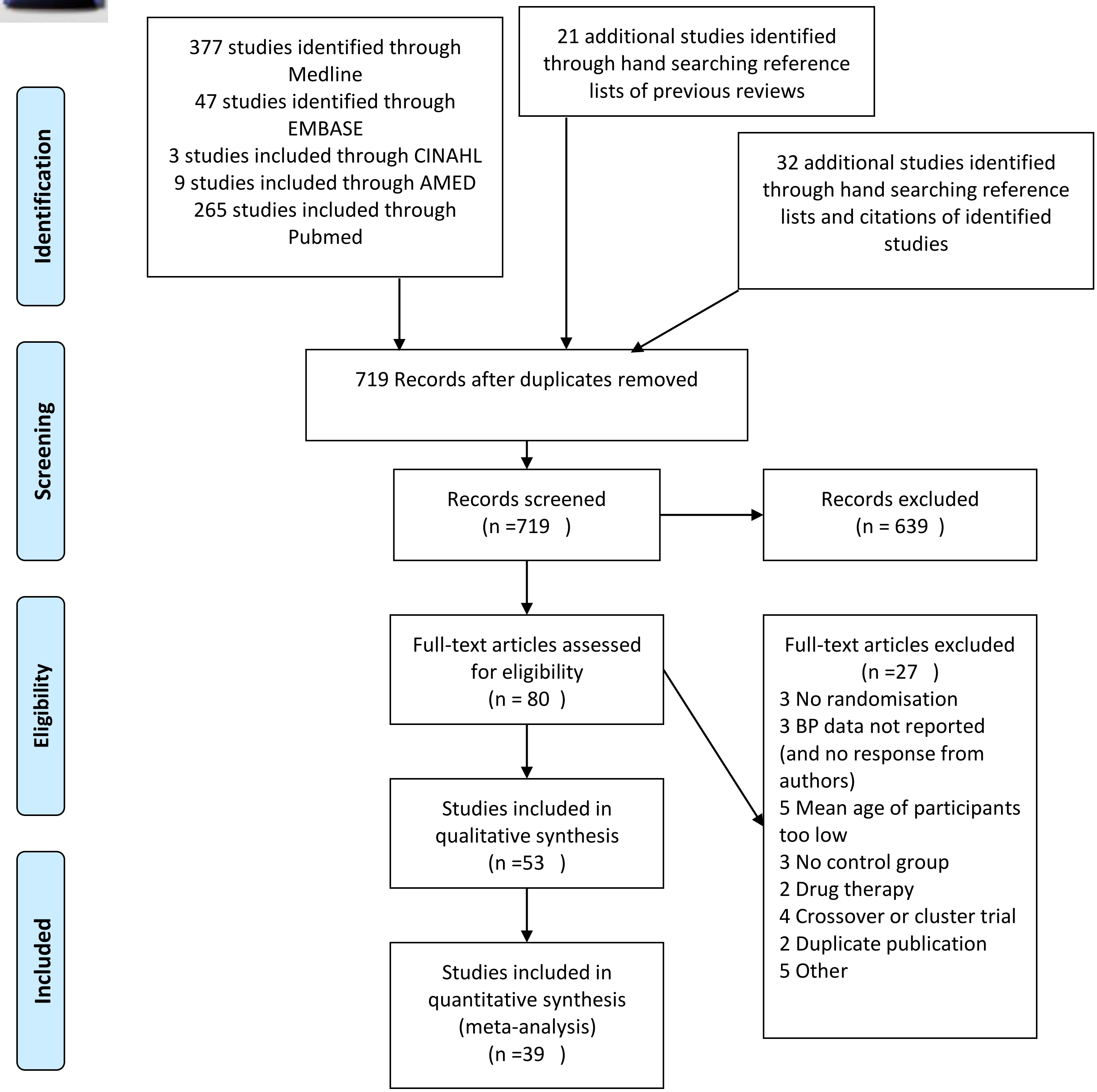
Valente 2011	27	41	67	Not specified	Obese (BMI 25-40) sedentary	Rested seated
Venturelli 2015	40	50	68	Hypertensive BP 140-159/90-99		not specified
Vincent 2003	62	45	68	BP < 160/100		Rested seated
Wang 2012	361	32	77	Not specified	sedentary	not specified
Westhoff 2007	54	48	68	isolated systolic hypertension (SBP>140 DBP <90)		24Hr Ambulatory
Westhoff 2008	24	46	67	Hypertensive (SBP >140 and/or taking antihypertensives)		not specified
Whelton 1998	975	Not specified	66	Hypertensive (BP <145/85 whilst taking antihypertensives)		Rested seated
Wood 2001	36	47	68	Not specified		not specified
Yassine 2009	24	36	66	Not specified	Obese (BMI30-40) and sedentary	Rested seated
Young 1999	62	21	67	Hypertensive (BP130-159/<95)	not taking antihypertensives	Rested seated

Legends for figures

1. Figure 1: PRISMA flow diagram
2. Figure 2: Risk of bias of included studies
3. Figure 3: Aerobic exercise SBP Forest plot
4. Figure 4: Aerobic exercise DBP Forest plot
5. Figure 5: Resistance exercise SBP Forest plot
6. Figure 6: Resistance exercise DBP Forest plot
7. Figure 7: Combined Aerobic and Resistance exercise SBP Forest plot
8. Figure 8: Combined Aerobic and Resistance exercise DBP Forest plot

List of supplementary digital content

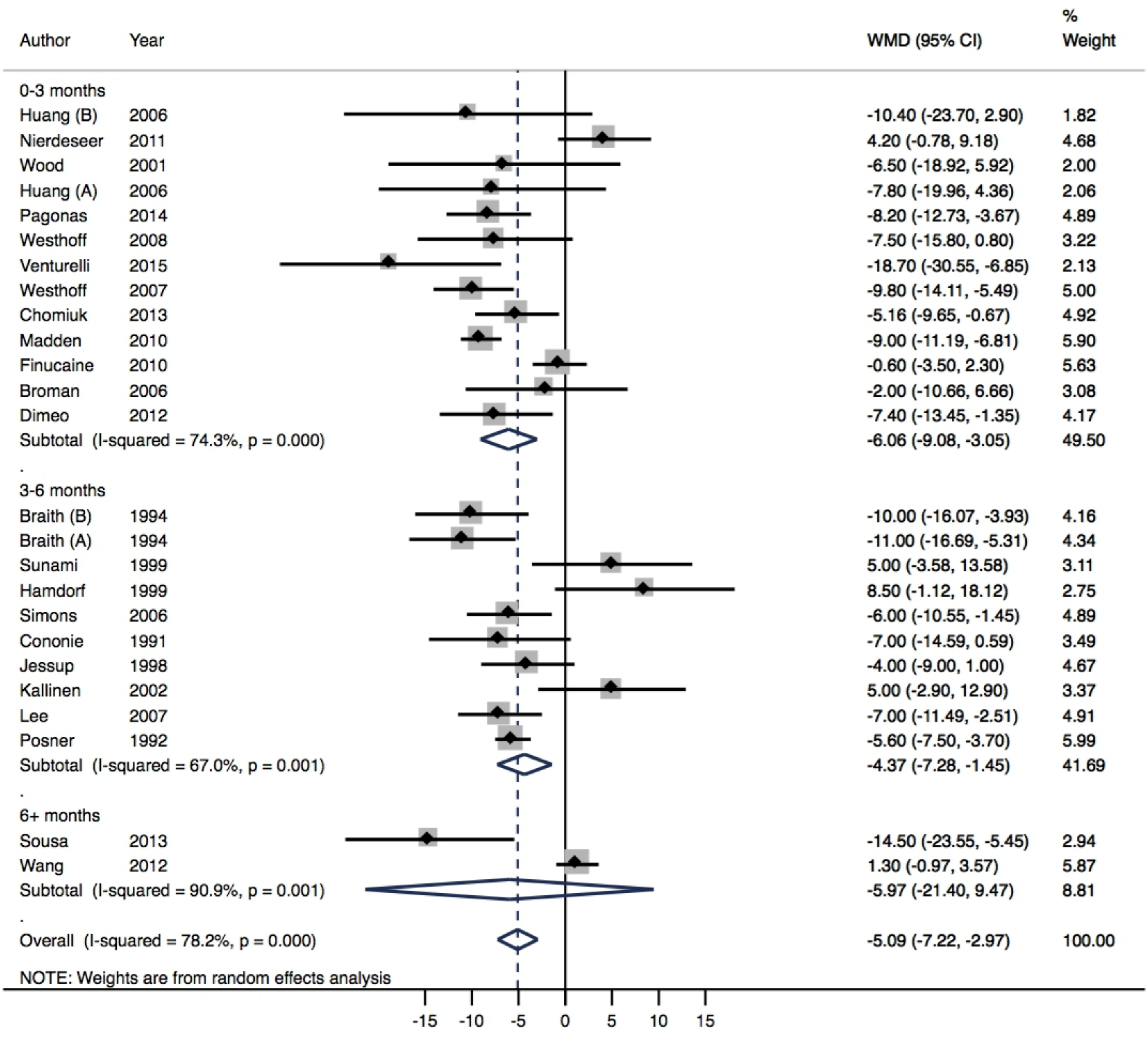
PRISMA 2009 Flow Diagram



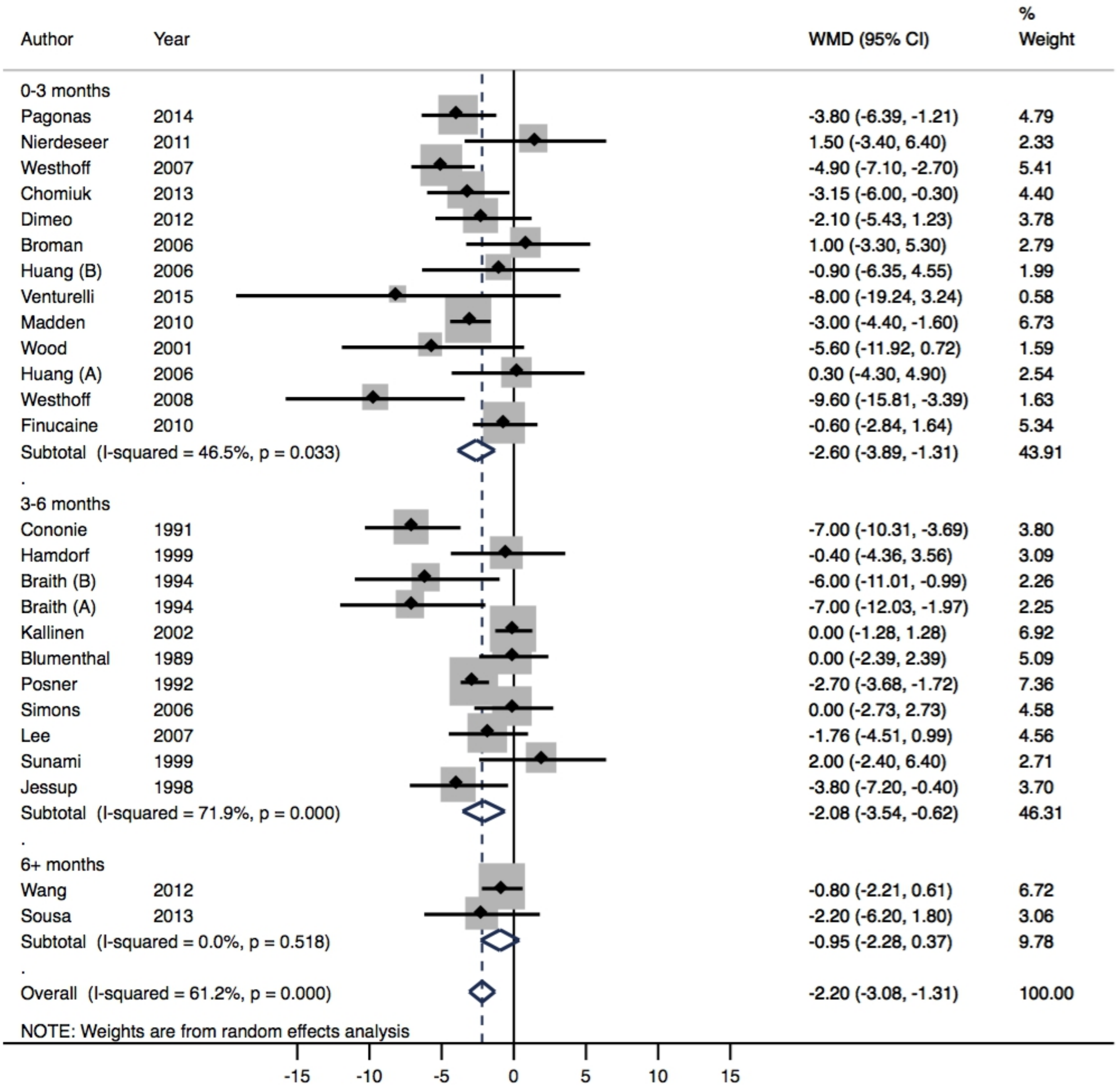
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Applegate 1992	?	?	−	+	−	?	+
Barone 2009	?	?	−	?	+	?	+
Blumenthal 1989	?	?	−	?	+	?	−
Bouchonville 2014	+	?	−	?	+	−	+
Braith 1994	?	?	−	?	+	?	−
Broman 2006	?	?	−	?	−	?	−
Chomiuk 2013	?	?	−	?	+	?	+
Cononie 1991	−	?	−	?	−	?	?
Dimeo 2012	+	?	−	+	+	?	+
Dusek 2008	+	+	?	+	+	+	+
Faulkner 2013	+	+	−	+	+	+	−
Finucane 2010	+	?	−	+	+	+	−
Gerage 2012	?	?	−	?	+	?	+
Goncalves 2014	?	?	−	?	?	?	−
Hamdorf 1999	+	?	−	?	−	?	+
Huang 2006	?	?	−	+	−	?	−
Jessup 2008	?	?	−	?	+	?	+
Kallinen 2002	+	?	−	?	−	?	−
Lee 2007	+	+	−	+	+	?	+
Li 2003	+	+	−	?	−	?	−
Li 2005	+	+	−	−	+	?	+
Lim 2015	?	?	−	?	+	?	+
Lovell 2009	?	?	−	?	+	?	+
Madden 2009	?	+	−	+	+	+	−
Mayneris-Perxachs 2014	+	+	−	+	+	−	?
Millar 2008	?	−	−	?	+	?	−
Miura 2015	?	?	−	?	−	?	+
Mota 2013	−	?	−	?	?	?	+
Nestel 1993	?	?	?	?	+	?	+
Niederseer 2011	?	?	−	?	?	?	−
Nishijima 2007	+	?	−	?	+	+	+
Ohkubo 2001	+	+	−	−	−	?	+
Okumiya 1996	?	?	−	+	+	?	−
Pagonas 2014	+	?	−	+	+	?	+
Patil 2015	+	−	−	?	+	−	+
Posner 1992	?	?	−	?	?	?	+
Puggard 2000	−	−	−	?	−	?	−
Simons 2006	?	?	−	+	+	?	−
Sousa 2013	?	?	−	?	−	?	−
Stachenfeld 1998	?	?	−	?	−	?	+
Sunami 1999	?	?	−	?	+	?	+
Taylor 2003	?	?	−	?	+	?	−
Teng 2007	?	?	−	?	−	?	−
Thomas 2005	+	?	−	?	+	?	+
Tsutsumi 1997	?	?	−	?	+	?	−
Valente 2011	?	?	−	?	−	?	−
Venturelli 2015	?	?	−	+	+	?	+
Vincent 2002	+	?	−	?	−	?	−
Wang 2012	+	+	−	+	?	−	+
Westhoff 2007	+	?	−	?	−	+	+
Westhoff 2008	?	?	−	?	+	?	+
Whelton 1998	+	?	−	+	+	?	+
Wood 2001	?	?	−	?	−	?	+
Yassine 2009	?	?	−	?	+	?	+
Young 1999	+	?	−	+	+	?	+



Author Year
WMD (95% CI)
% Weight
0-3 months
Huang (B) 2006 -10.40 (-23.70, 2.90) 1.82
Nierdeseer 2011 4.20 (-0.78, 9.18) 4.68
Wood 2001 -6.50 (-18.92, 5.92) 2.00
Huang (A) 2006 -7.80 (-19.96, 4.36) 2.06
Pagonas 2014 -8.20 (-12.73, -3.67) 4.89
Westhoff 2008 -7.50 (-15.80, 0.80) 3.22
Venturelli 2015 -18.70 (-30.55, -6.85) 2.13
Westhoff 2007 -9.80 (-14.11, -5.49) 5.00
Chomiuk 2013 -5.16 (-9.65, -0.67) 4.92
Madden 2010 -9.00 (-11.19, -6.81) 5.90
Finucaine 2010 -0.60 (-3.50, 2.30) 5.63
Broman 2006 -2.00 (-10.66, 6.66) 3.08
Dimeo 2012 -7.40 (-13.45, -1.35) 4.17
Subtotal (I-squared = 74.3%, p = 0.000) -6.06 (-9.08, -3.05) 49.50
.
3-6 months
Braith (B) 1994 -10.00 (-16.07, -3.93) 4.16
Braith (A) 1994 -11.00 (-16.69, -5.31) 4.34
Sunami 1999 5.00 (-3.58, 13.58) 3.11
Hamdorf 1999 8.50 (-1.12, 18.12) 2.75
Simons 2006 -6.00 (-10.55, -1.45) 4.89
Cononie 1991 -7.00 (-14.59, 0.59) 3.49
Jessup 1998 -4.00 (-9.00, 1.00) 4.67
Kallinen 2002 5.00 (-2.90, 12.90) 3.37
Lee 2007 -7.00 (-11.49, -2.51) 4.91
Posner 1992 -5.60 (-7.50, -3.70) 5.99
Subtotal (I-squared = 67.0%, p = 0.001) -4.37 (-7.28, -1.45) 41.69
.
6+ months
Sousa 2013 -14.50 (-23.55, -5.45) 2.94
Wang 2012 1.30 (-0.97, 3.57) 5.87
Subtotal (I-squared = 90.9%, p = 0.001) -5.97 (-21.40, 9.47) 8.81
.
Overall (I-squared = 78.2%, p = 0.000) -5.09 (-7.22, -2.97) 100.00
NOTE: Weights are from random effects analysis
-15 -10 -5 0 5 10 15



Author
Year
WMD (95% CI)
% Weight
0-3 months
Pagonas 2014 -3.80 (-6.39, -1.21) 4.79
Nierdeseer 2011 1.50 (-3.40, 6.40) 2.33
Westhoff 2007 -4.90 (-7.10, -2.70) 5.41
Chomiuk 2013 -3.15 (-6.00, -0.30) 4.40
Dimeo 2012 -2.10 (-5.43, 1.23) 3.78
Broman 2006 1.00 (-3.30, 5.30) 2.79
Huang (B) 2006 -0.90 (-6.35, 4.55) 1.99
Venturelli 2015 -8.00 (-19.24, 3.24) 0.58
Madden 2010 -3.00 (-4.40, -1.60) 6.73
Wood 2001 -5.60 (-11.92, 0.72) 1.59
Huang (A) 2006 0.30 (-4.30, 4.90) 2.54
Westhoff 2008 -9.60 (-15.81, -3.39) 1.63
Finucaine 2010 -0.60 (-2.84, 1.64) 5.34
Subtotal (I-squared = 46.5%, p = 0.033) -2.60 (-3.89, -1.31) 43.91
.
3-6 months
Cononie 1991 -7.00 (-10.31, -3.69) 3.80
Hamdorf 1999 -0.40 (-4.36, 3.56) 3.09
Braith (B) 1994 -6.00 (-11.01, -0.99) 2.26
Braith (A) 1994 -7.00 (-12.03, -1.97) 2.25
Kallinen 2002 0.00 (-1.28, 1.28) 6.92
Blumenthal 1989 0.00 (-2.39, 2.39) 5.09
Posner 1992 -2.70 (-3.68, -1.72) 7.36
Simons 2006 0.00 (-2.73, 2.73) 4.58
Lee 2007 -1.76 (-4.51, 0.99) 4.56
Sunami 1999 2.00 (-2.40, 6.40) 2.71
Jessup 1998 -3.80 (-7.20, -0.40) 3.70
Subtotal (I-squared = 71.9%, p = 0.000) -2.08 (-3.54, -0.62) 46.31
.
6+ months
Wang 2012 -0.80 (-2.21, 0.61) 6.72
Sousa 2013 -2.20 (-6.20, 1.80) 3.06
Subtotal (I-squared = 0.0%, p = 0.518) -0.95 (-2.28, 0.37) 9.78
.
Overall (I-squared = 61.2%, p = 0.000) -2.20 (-3.08, -1.31) 100.00
NOTE: Weights are from random effects analysis
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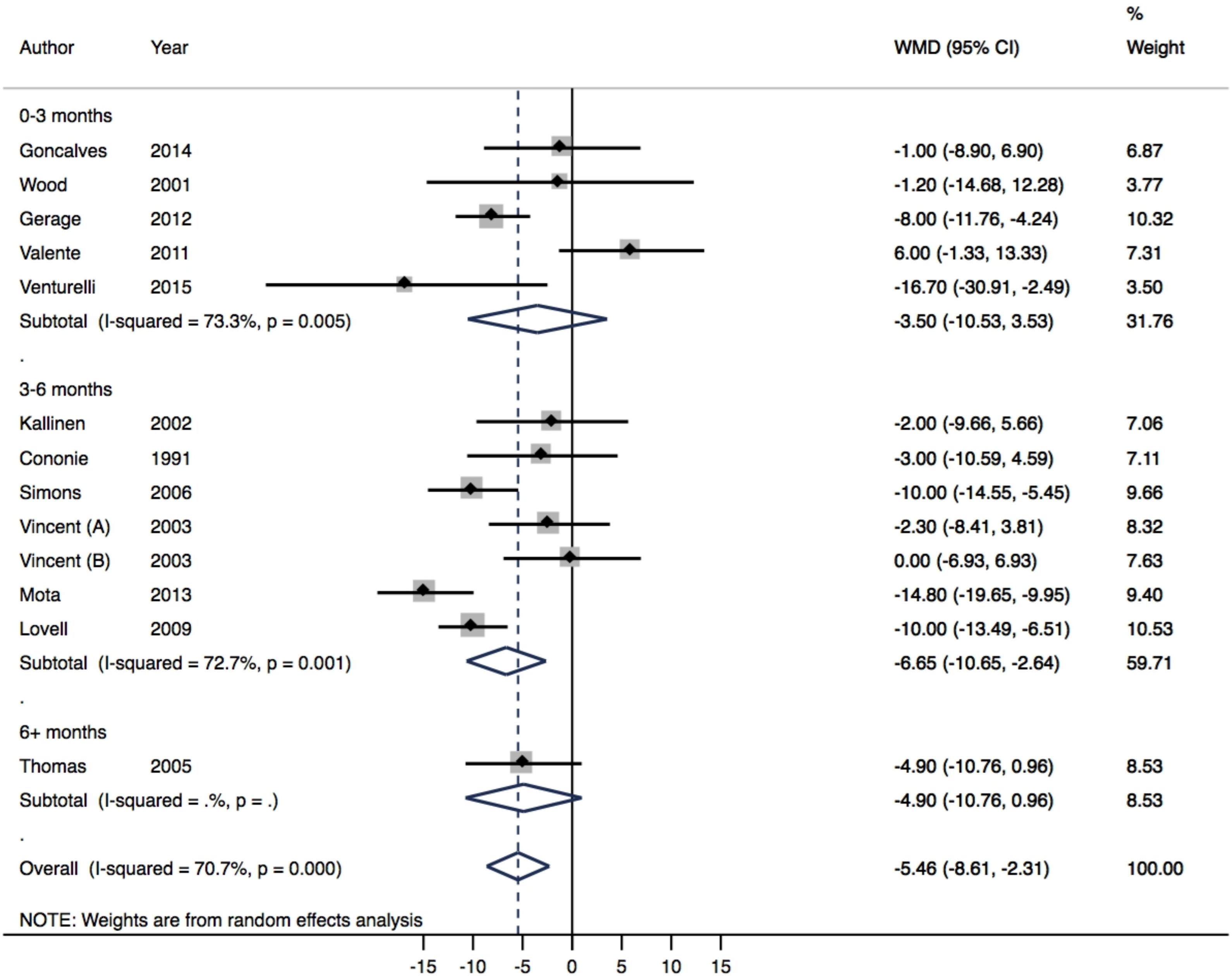
-10
-5
0
5
10
15



Author
Year
WMD (95% CI)
% Weight
0-3 months
Goncalves 2014 -1.00 (-8.90, 6.90) 6.87
Wood 2001 -1.20 (-14.68, 12.28) 3.77
Gerage 2012 -8.00 (-11.76, -4.24) 10.32
Valente 2011 6.00 (-1.33, 13.33) 7.31
Venturelli 2015 -16.70 (-30.91, -2.49) 3.50
Subtotal (I-squared = 73.3%, p = 0.005) -3.50 (-10.53, 3.53) 31.76
.
3-6 months
Kallinen 2002 -2.00 (-9.66, 5.66) 7.06
Cononie 1991 -3.00 (-10.59, 4.59) 7.11
Simons 2006 -10.00 (-14.55, -5.45) 9.66
Vincent (A) 2003 -2.30 (-8.41, 3.81) 8.32
Vincent (B) 2003 0.00 (-6.93, 6.93) 7.63
Mota 2013 -14.80 (-19.65, -9.95) 9.40
Lovell 2009 -10.00 (-13.49, -6.51) 10.53
Subtotal (I-squared = 72.7%, p = 0.001) -6.65 (-10.65, -2.64) 59.71
.
6+ months
Thomas 2005 -4.90 (-10.76, 0.96) 8.53
Subtotal (I-squared = .%, p = .) -4.90 (-10.76, 0.96) 8.53
.
Overall (I-squared = 70.7%, p = 0.000) -5.46 (-8.61, -2.31) 100.00
NOTE: Weights are from random effects analysis
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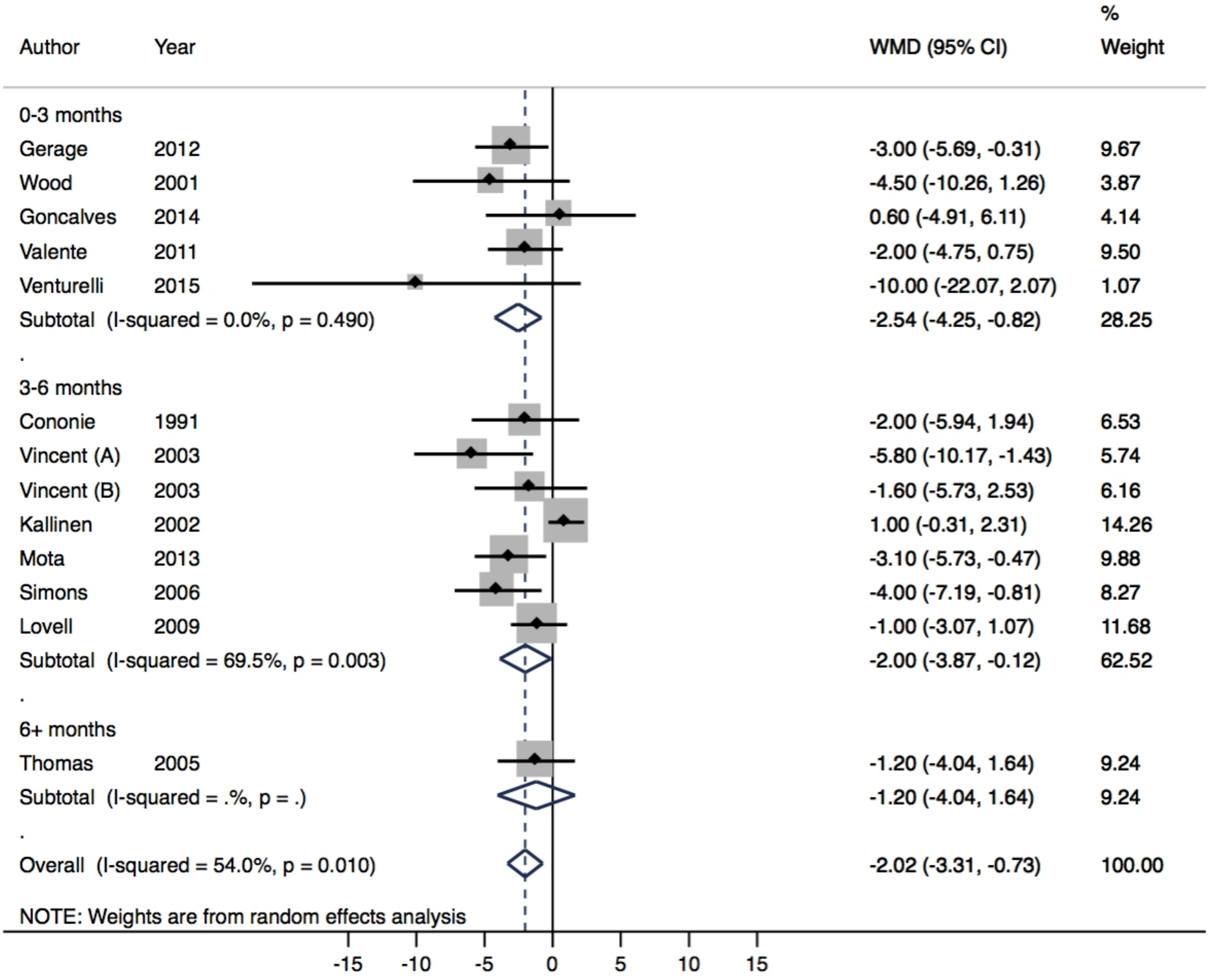
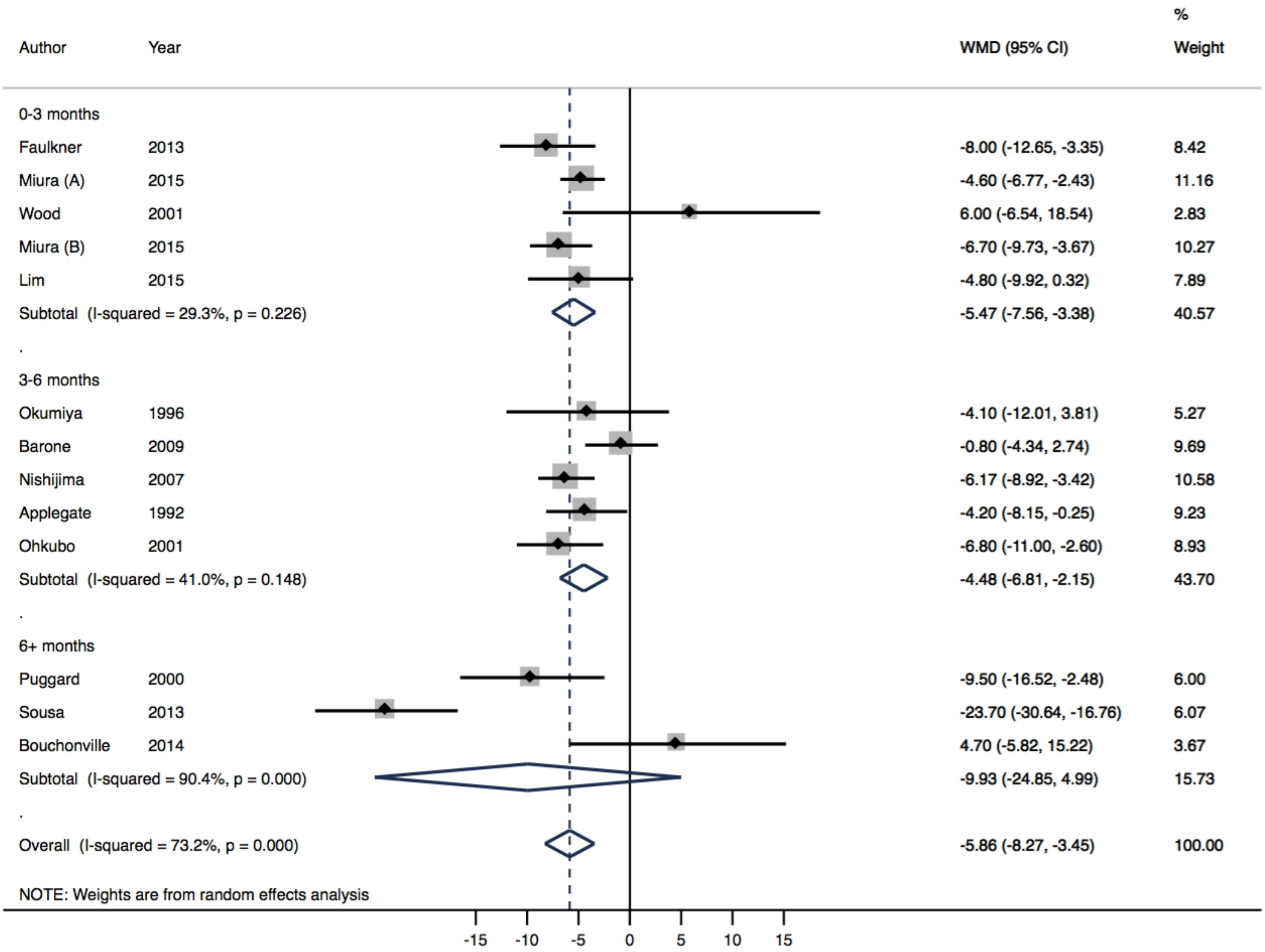

Author
Year
WMD (95% CI)
% Weight
0-3 months
Gerage 2012 -3.00 (-5.69, -0.31) 9.67
Wood 2001 -4.50 (-10.26, 1.26) 3.87
Goncalves 2014 0.60 (-4.91, 6.11) 4.14
Valente 2011 -2.00 (-4.75, 0.75) 9.50
Venturelli 2015 -10.00 (-22.07, 2.07) 1.07
Subtotal (I-squared = 0.0%, p = 0.490) -2.54 (-4.25, -0.82) 28.25
.
3-6 months
Cononie 1991 -2.00 (-5.94, 1.94) 6.53
Vincent (A) 2003 -5.80 (-10.17, -1.43) 5.74
Vincent (B) 2003 -1.60 (-5.73, 2.53) 6.16
Kallinen 2002 1.00 (-0.31, 2.31) 14.26
Mota 2013 -3.10 (-5.73, -0.47) 9.88
Simons 2006 -4.00 (-7.19, -0.81) 8.27
Lovell 2009 -1.00 (-3.07, 1.07) 11.68
Subtotal (I-squared = 69.5%, p = 0.003) -2.00 (-3.87, -0.12) 62.52
.
6+ months
Thomas 2005 -1.20 (-4.04, 1.64) 9.24
Subtotal (I-squared = .%, p = .) -1.20 (-4.04, 1.64) 9.24
.
Overall (I-squared = 54.0%, p = 0.010) -2.02 (-3.31, -0.73) 100.00
NOTE: Weights are from random effects analysis
-15
-10
-5
0
5
10
15


Author
Year
WMD (95% CI)
%
Weight
0-3 months
Faulkner 2013 -8.00 (-12.65, -3.35) 8.42
Miura (A) 2015 -4.60 (-6.77, -2.43) 11.16
Wood 2001 6.00 (-6.54, 18.54) 2.83
Miura (B) 2015 -6.70 (-9.73, -3.67) 10.27
Lim 2015 -4.80 (-9.92, 0.32) 7.89
Subtotal (I-squared = 29.3%, p = 0.226) -5.47 (-7.56, -3.38) 40.57
.
3-6 months
Okumiya 1996 -4.10 (-12.01, 3.81) 5.27
Barone 2009 -0.80 (-4.34, 2.74) 9.69
Nishijima 2007 -6.17 (-8.92, -3.42) 10.58
Applegate 1992 -4.20 (-8.15, -0.25) 9.23
Ohkubo 2001 -6.80 (-11.00, -2.60) 8.93
Subtotal (I-squared = 41.0%, p = 0.148) -4.48 (-6.81, -2.15) 43.70
.
6+ months
Puggard 2000 -9.50 (-16.52, -2.48) 6.00
Sousa 2013 -23.70 (-30.64, -16.76) 6.07
Bouchonville 2014 4.70 (-5.82, 15.22) 3.67
Subtotal (I-squared = 90.4%, p = 0.000) -9.93 (-24.85, 4.99) 15.73
.
Overall (I-squared = 73.2%, p = 0.000) -5.86 (-8.27, -3.45) 100.00
NOTE: Weights are from random effects analysis
-15
-10
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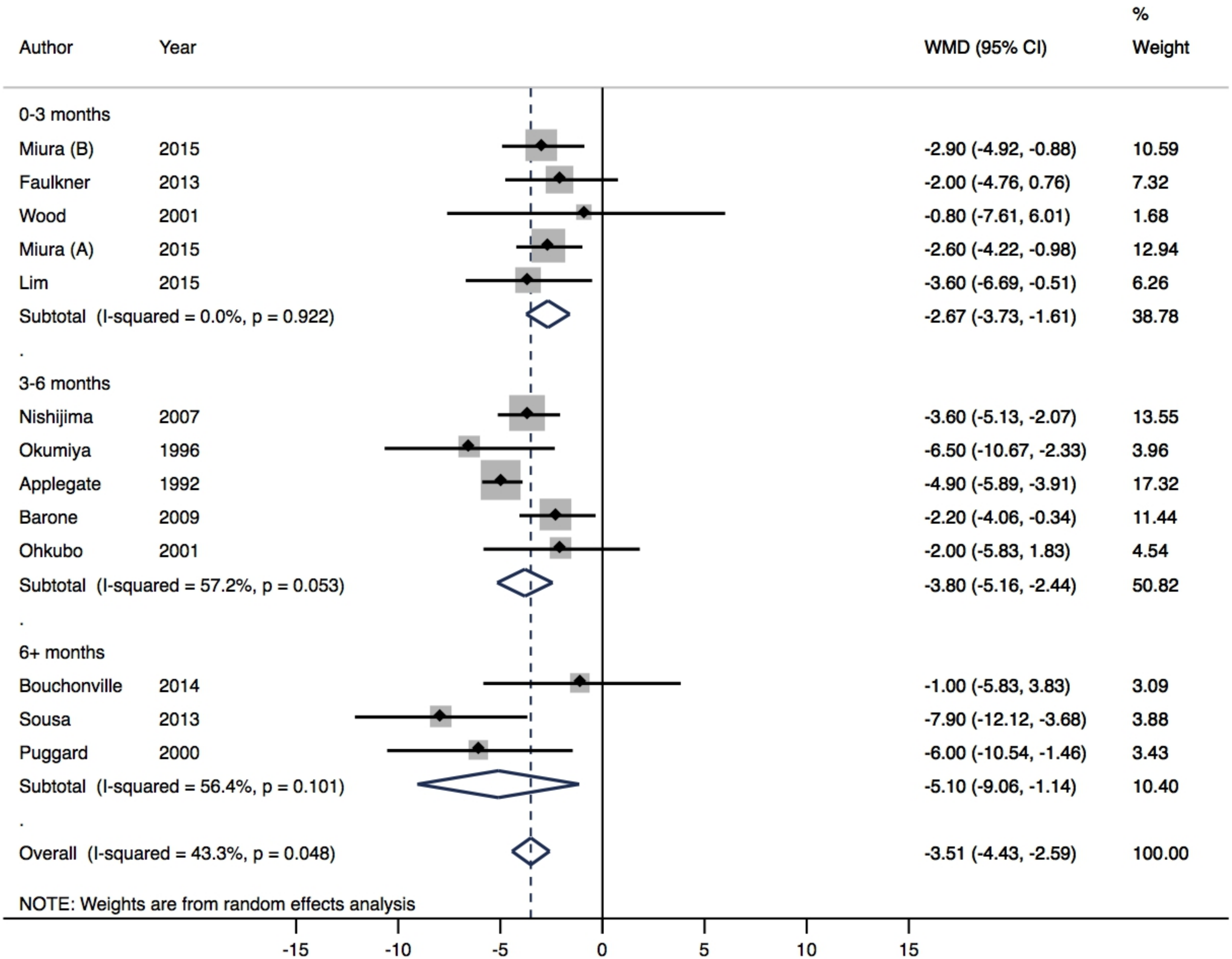
15



%
Author
Year
WMD (95% CI)
Weight
0-3 months
Miura (B) 2015 -2.90 (-4.92, -0.88) 10.59
Faulkner 2013 -2.00 (-4.76, 0.76) 7.32
Wood 2001 -0.80 (-7.61, 6.01) 1.68
Miura (A) 2015 -2.60 (-4.22, -0.98) 12.94
Lim 2015 -3.60 (-6.69, -0.51) 6.26
Subtotal (I-squared = 0.0%, p = 0.922) -2.67 (-3.73, -1.61) 38.78
3-6 months
Nishijima 2007 -3.60 (-5.13, -2.07) 13.55
Okumiya 1996 -6.50 (-10.67, -2.33) 3.96
Applegate 1992 -4.90 (-5.89, -3.91) 17.32
Barone 2009 -2.20 (-4.06, -0.34) 11.44
Ohkubo 2001 -2.00 (-5.83, 1.83) 4.54
Subtotal (I-squared = 57.2%, p = 0.053) -3.80 (-5.16, -2.44) 50.82
6+ months
Bouchonville 2014 -1.00 (-5.83, 3.83) 3.09
Sousa 2013 -7.90 (-12.12, -3.68) 3.88
Puggard 2000 -6.00 (-10.54, -1.46) 3.43
Subtotal (I-squared = 56.4%, p = 0.101) -5.10 (-9.06, -1.14) 10.40
Overall (I-squared = 43.3%, p = 0.048) -3.51 (-4.43, -2.59) 100.00
NOTE: Weights are from random effects analysis
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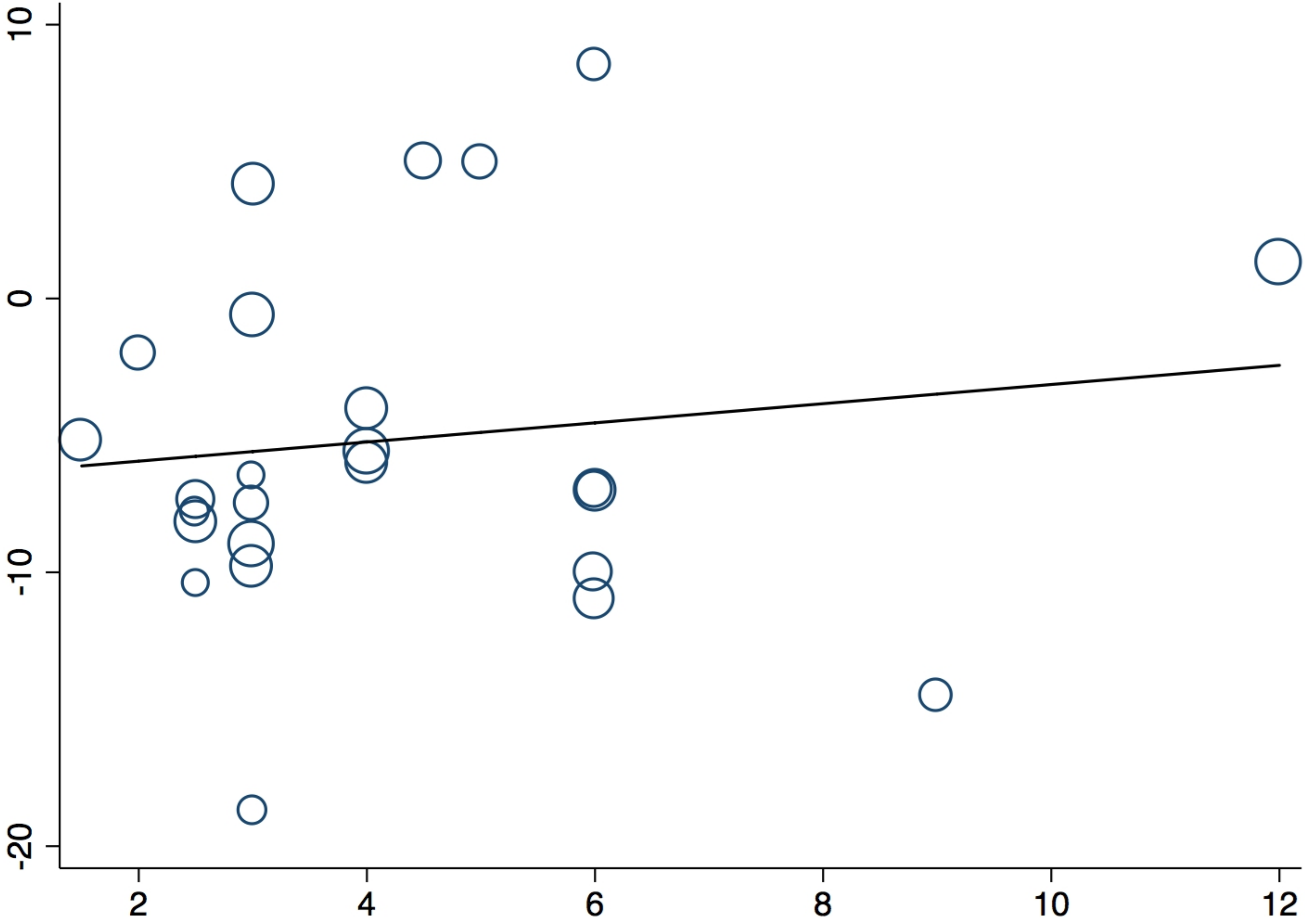
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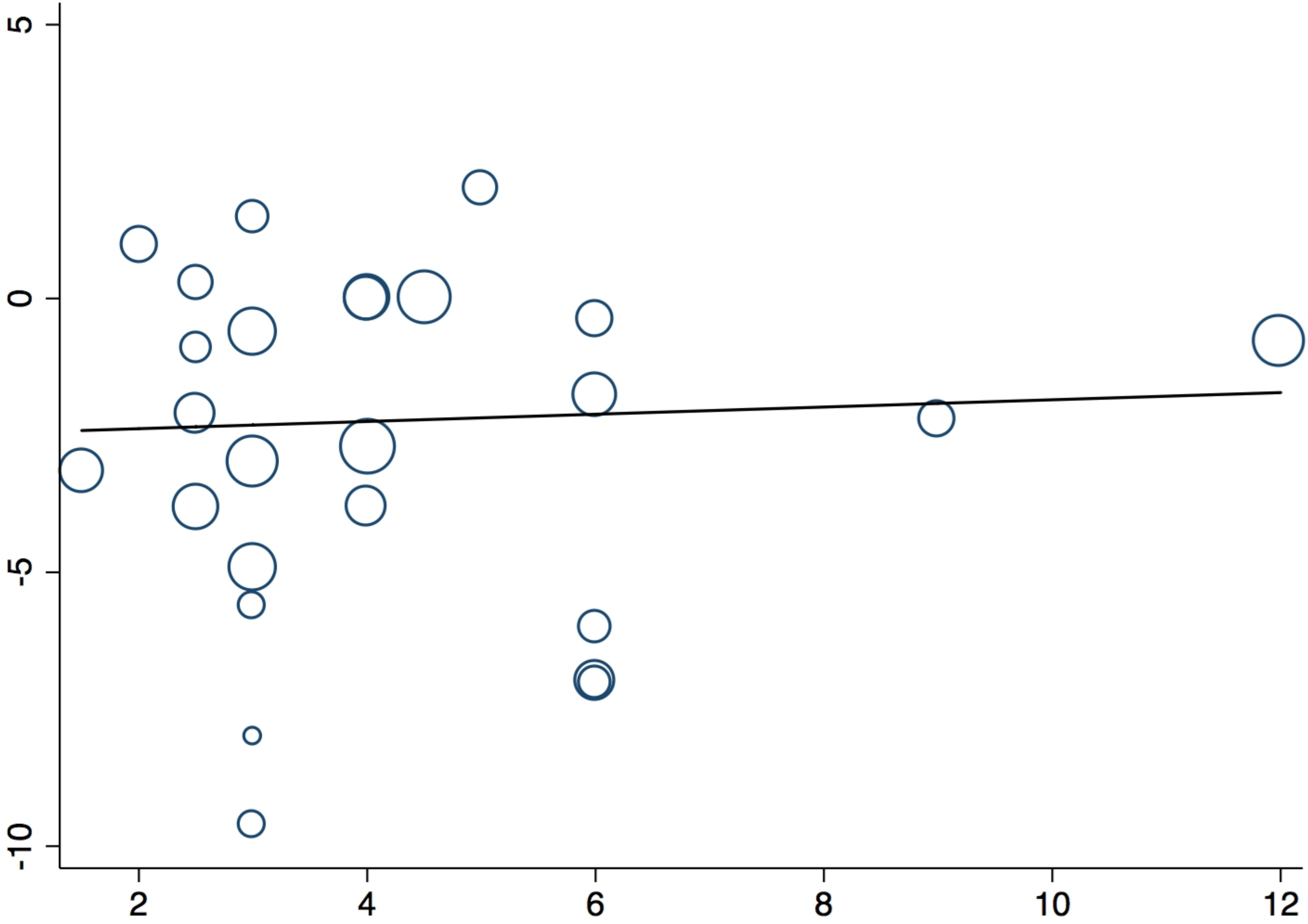
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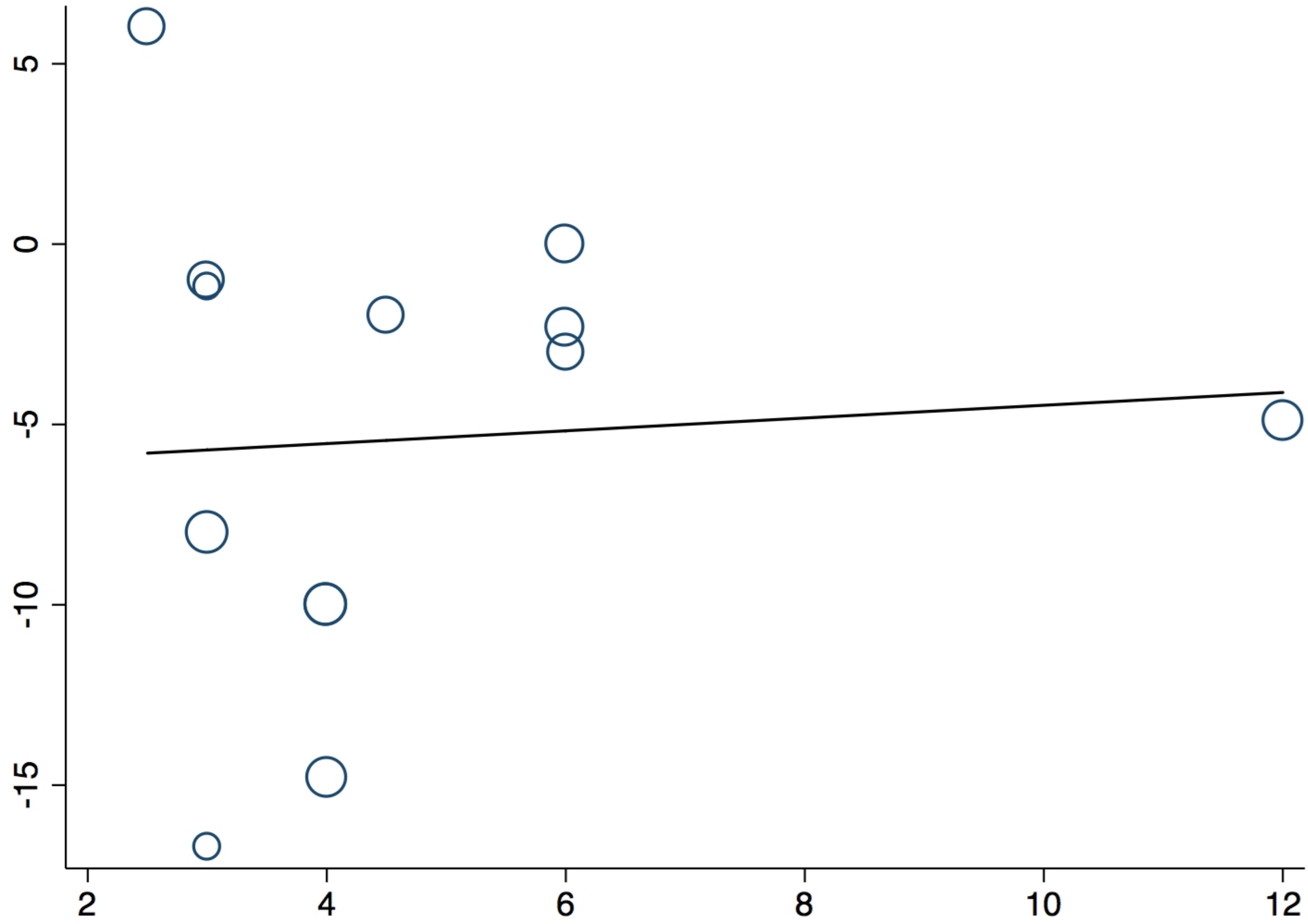

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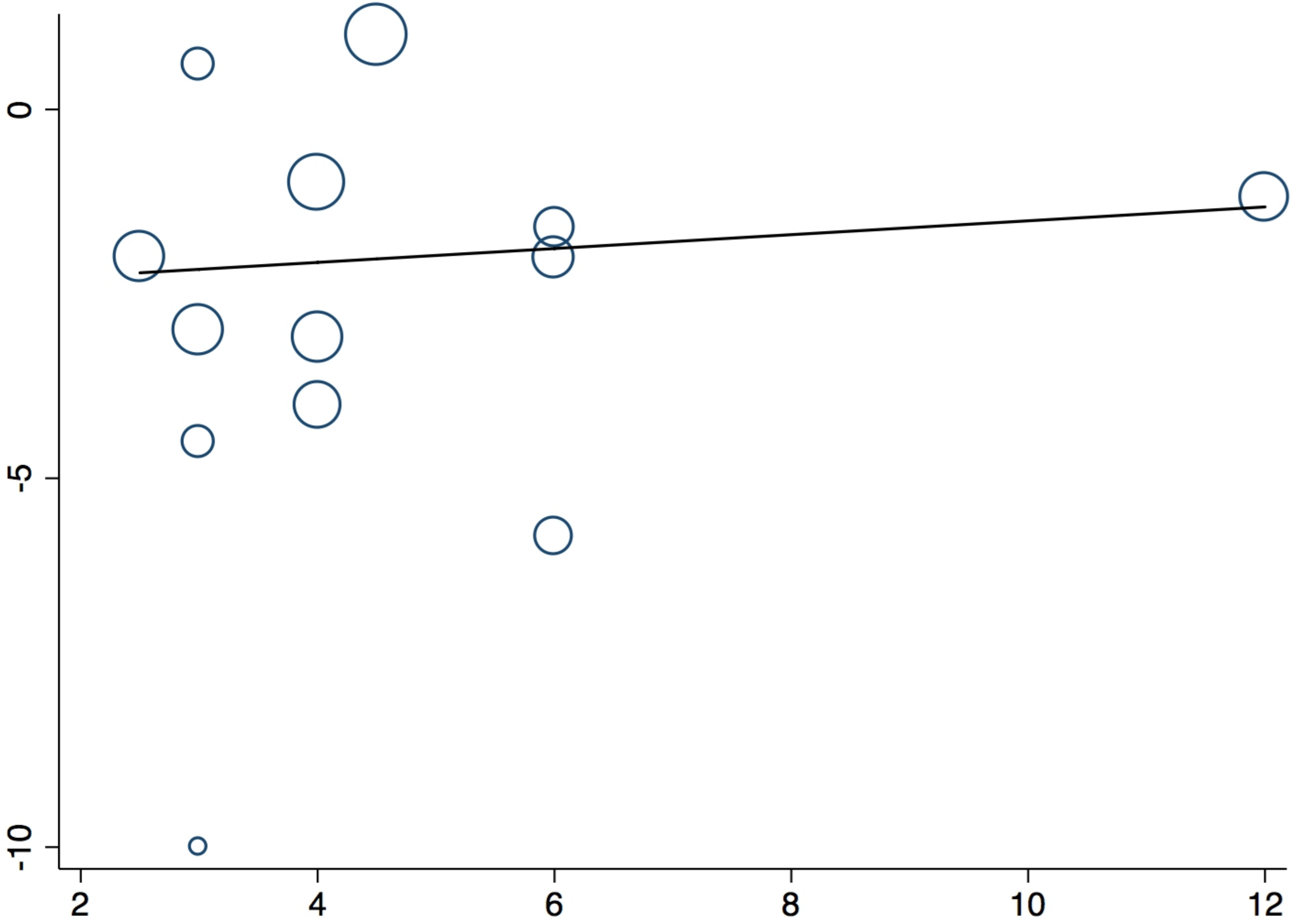

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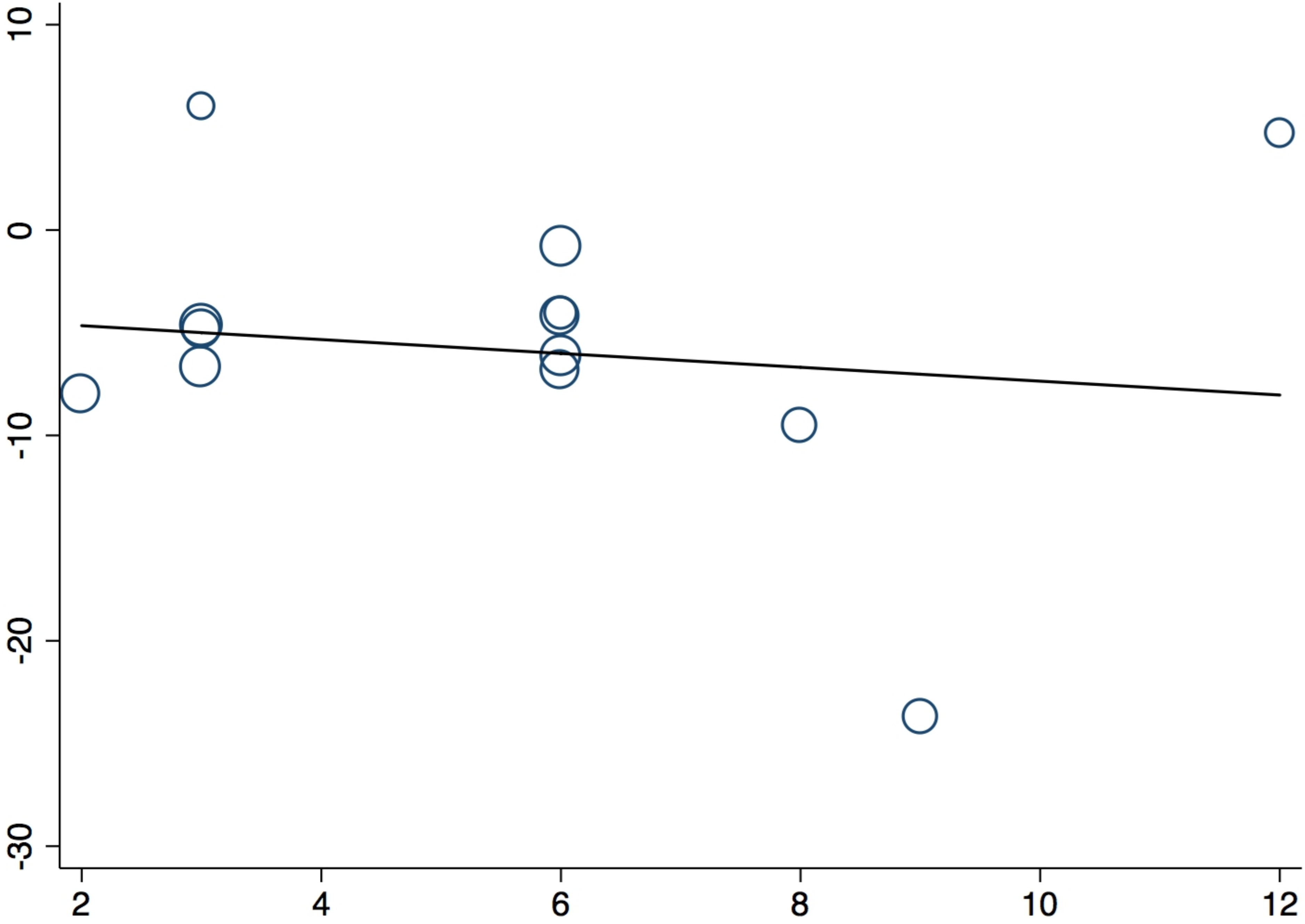

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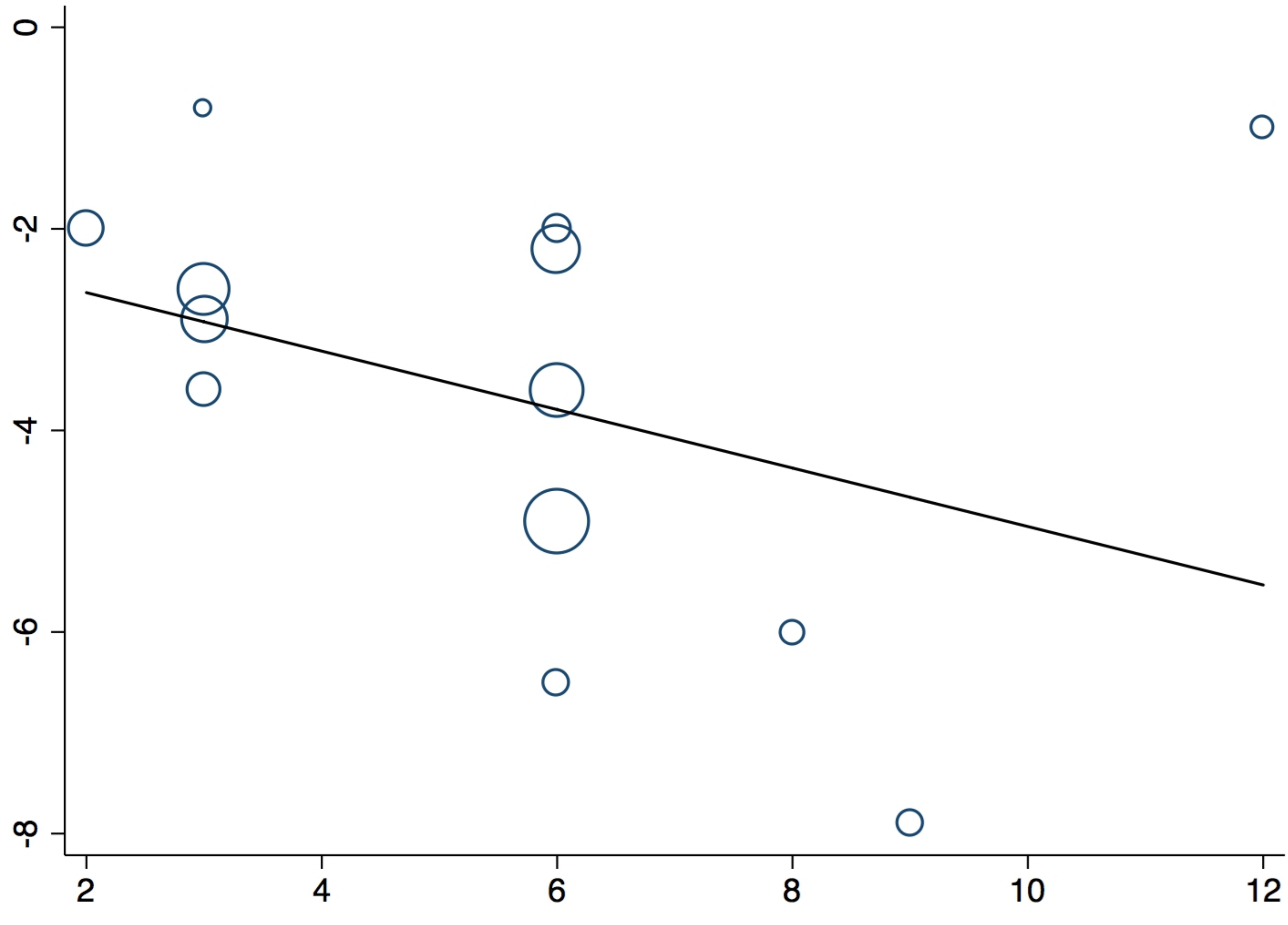
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