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Effect of Multi-Modal Therapies for Kinesiophobia Caused by Musculoskeletal Disorders: A Systematic Review and Meta-Analysis

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Abstract: This systematic review and meta-analysis aimed to identify the effect of multi-modal therapies that combined physical and psychological therapies for kinesiophobia caused by musculoskeletal disorders compared with uni-modal therapy of only phycological therapy The search terms and their logical connector were as following: or psychological therapy. (1) "kinesiophobia" at the title or abstract; and (2) "randomized" OR "randomized" at title or abstract; not (3) "design" OR "protocol" at the title. They were typed into the databases of Medline (EBSCO), PubMed, and Ovid, following the different input rules of these databases. The eligibility criteria were: (1) Adults with musculoskeletal disorders or illness as patients; (2) Multi-modal therapies combined physical and psychological therapy as interventions; (3) Uni-modal therapy of only physical or psychological therapy as a comparison; (4) The scores of the 17-items version of the Tampa Scale of Kinesiophobia as the outcome; (5) Randomized controlled trials as study design. As a result, 12 studies were included with a statistically significant polled effect of 6.99 (95% CI 4.59 to 9.38). Despite a large heterogeneity within studies, multi-modal therapies might be more effective in reducing kinesiophobia than the unimodal of only physical or psychological therapy both in the total and subdivision analysis. The effect might decrease with age. What's more, this review's mathematical methods were feasible by taking test-retest reliability of the Tampa Scale of Kinesiophobia into consideration.

Keywords: kinesiophobia; pain; multi-modal; psychological measure; Tampa scale

1. Introduction

Musculoskeletal disorders and the following pain were common in most people's daily life [1], and the musculoskeletal pain caused by musculoskeletal disorders was the second most common cause of disability [2]. Many established factors, such as physical, biological, cognitive, behavioral, social, and occupation, were correlated with the pain following musculoskeletal disorders [1,3,4].

Fear was considered to be an explanation of why pain and associated outcomes such as disability persist once the body injury had healed [5,6], and the fear-avoidance model of pain was one of the frameworks which could explain the development and persistence of the pain and disability following a musculoskeletal injury [7,8]. According to this model, people with a trait tend to have fear and catastrophic thoughts in response to pain were more at risk of developing chronic musculoskeletal pain after an injury than people who did not have this tendency [6,8]. These people over-reacted in response to actual or potential threats, developing avoidance behaviors to prevent a new injury/re-injury [6]. Fear

in relation to pain had been described with various conceptual definitions, among which pain-related fear, fear-avoidance beliefs, fear of movement, and kinesiophobia were the most commonly used [9].

Kinesiophobia was one of the most commonly used conceptual definitions which could describe fear in relation to pain [10]. Kinesiophobia (also known as the fear of movement) was defined as an excessive, irrational, and debilitating fear to carry out a physical movement due to a feeling of vulnerability to a painful injury or re-injury [10]. It could be acquired through a direct aversive experience such as pain and trauma or through social learning such as observation and instruction [11]. Kinesiophobia had been associated with pain, disability, and quality of daily life to some extent [12]. The prevalence of kinesiophobia in chronic pain was from 50% to 70% [13,14].

The objective of rehabilitation is to recover physical exercises' performance, regain the capacity of daily activities, and restore social functions. In recent years, studies on the rehabilitation of musculoskeletal disorders had begun to focus on the fear in relation to pain [15,16]. The fear in relation to pain would cause people to produce fear-avoidance and had a negative effect on their quality of life. Therefore, not only the rehabilitation at the physical level but also the rehabilitation at the psychological level should be paid attention to [17–20]. At the same time, as mentioned above, kinesiophobia could be acquired through many different ways (e.g., personal experience, social learning) [11], therapies combined multi-modal from both psychological and physical perspectives had become increasingly popular [15,21,22]. However, at present, only a few studies focus on the advantage of multi-modal therapies over uni-modal therapies, and most of the studies on the rehabilitation of musculoskeletal disorders were limited to specific musculoskeletal disorders. There was a lack of high-quality evidence from the macro-perspective. To answer this question, the terms "physical therapy" and "psychological therapy" should be defined in this review at first.

In this review, the terms "physical therapy" and "psychological therapy" were defined as follows. "Physical therapy" was the therapy included: (1) exercise/training session or advice with a private plan; (2) passive physical therapies such as usual care; (3) treatments provided by professional therapists or medical staff without any psychological education. It should be emphasized that exercise/training advice without a private plan, waiting lists and interventions without any control, such as keeping normal daily life, would be excluded.

"Psychological therapy" was the therapy include (1) psychological education; (2) cognition-behavior therapy; (3) perceptive stimulation in non-injured body areas such as virtual reality equipment, laser, and relaxation; (4) therapeutic milieu involves interpersonal communication such as group session and feedback session. It should be emphasized that if the doctor-patient communication in the intervention involved only an explanation of the treatment or only guidance of exercise or only supervision in training, the intervention wouldn't be regarded as psychological therapy.

Moreover, a quantitative indicator was required to assess the fear of movement, and there was not a specific tool to assess fear of movement directly [9]. The term "kinesiophobia" would be used. People with kinesiophobia would change their movements to avoid pain and adjust their motor behaviors [12]. The processing of pain and pain-related information in people with musculoskeletal disorders could be related to how kinesiophobia was perceived [23]. Therefore, a greater degree of kinesiophobia predicted greater levels of fear of pain and a great inclination to avoid physical movements [24].

Kinesiophobia could be measured by the Tampa Scale of Kinesiophobia (TSK) [25]. Since the Tampa Scale of Kinesiophobia had good validity in the quantization of kinesiophobia, the change of TSK scores would reflect the effect of therapy and be taken as a comparative indicator of therapy effect to some extent [26,27]. In the original version of the Tampa Scale of Kinesiophobia, participants would be asked to respond to how much they agreed with each of the 17 items, and the ratings available were: (1) disagree; (2) partially disagree; (3) partially agree; (4) strongly agree. The score of each item varies from 1–4 or 0–3. The responses were summed, and the generated score, which ranges from 17 to 68 or from 0 to 51 [13,25]. However, the TSK scores were usually reported as a secondary outcome, and that there was a limited number of studies that focus on the treatments for kinesiophobia. It made that a special study search strategy, information extraction, and data processing methods need to be applied.

This systematic review and meta-analysis aimed to identify the effect of multi-modal therapies, which combined physical and psychological therapies following the definition mentioned above, for kinesiphobia caused by musculoskeletal disorders compared with uni-modal therapies of an only physical or only psychological therapy that followed the definitions mentioned above.

2. Methods

2.1. Protocol and Registration

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Registration number: CRD42020218384) [28].

2.2. Eligibility and Exclusion Criteria And Rationale of PICOS

Studies were included in this review if they met the following eligibility criteria: (1) Patients should be adults with musculoskeletal disorders or illness. What should be emphasized was that the patients with the injuries and their following pain, which cause by surgery and other diseases of tissues and organs, would be excluded; (2) Intervention should be multi-modal therapy, which combined physical and psychological therapy. The definitions of physical therapy and psychological therapy were given in the introduction. For example, a cognitive-behavioral group intervention contained a skill training plan would be regarded as multi-modal therapy; (3) The comparison was multi-modal therapies versus uni-modal therapies. The uni-modal therapy should be physical therapy or psychological therapy, the definitions of which were given in the introduction. For example, a supervised home exercise with a given plan would be regarded as a uni-modal therapy from a physical perspective; (4) Outcomes would be scores of the 17-items version of the Tampa Scale of Kinesiophobia; (5) Randomized controlled trials; (6) Date and Language: published in English from inception to September 2020.

The 17-items Tampa Scale of Kinesiophobia had been demonstrated predictive and constructed validity as well as excellent test-retest reliability (0.64–0.91) and internal consistency (0.70–0.81). What should be paid attention to was that there were some shorten versions of the Tampa Scale of Kinesiophobia, such as TSK-11, TSK-13, and the Tampa Scale of Kinesiophobia for particular injuries. All of these versions demonstrated high validities, reliabilities, and consistencies as well. To ensure the consistency of results and reduce the heterogeneity, only the 17-items version would be chosen as this review's outcome, and the 17-items version whose scores ranged from 0 to 3 would be converted to 1 to 4.

Studies would be excluded if they met the following eligibility criteria: (1) Healthy people, children, and teenagers; (2) pain caused by trauma, burns, or surgery; (3) other versions of the Tampa Scale of Kinesiophobia; (4) lack of origin scores of the Tampa Scale of Kinesiophobia.

2.3. Search and Study Selection

The search terms and their logical connector were as following: (1) "kinesiophobia" at the title or abstract; and (2) "randomized" OR "randomized" at title or abstract; not (3) "design" OR "protocol" at the title. They were typed into the databases of Medline (EBSCO), PubMed, and Ovid, following the different input rules of these databases.

In the database PubMed, the search term"(kinesiophobia[Title/Abstract]) AND ((randomized) or (randomised)[Title/Abstract]) NOT ((design) or (protocol)[Title])" was used, then the results would be limited at "randomized controlled trials". In the database Medline (EBSCO), the search term "AB kinesiophobia and AB (randomized or randomised) NOT TI (design or protocol)" was used, and the range of search would be fixed in Cochrane Central Register of Trials, Medline with Full Text, and CINAHL. In the database Ovid, "All Resources" would be chosen, and the search term "(kinesiophobia and (randomized or randomised) .ab not (design or protocol).at" was used with the tool "Multi-Field

Search", and the language would be limited in English. All the results would be downloaded and imported into EndNote X9 for further screening.

With the help of the functions "deduplication" and "searching in library" of EndNote X9, the duplicated and ineligible studied would be screened.

A unified method and standard of study search and Selection were used, in which the two authors (Y.X. and Y.S.) searched the study in turn, independently. The figures and tables for information would be made after the two authors verified their results finally. An independent arbitrator (D.S) resolved any discrepancies in data extraction.

2.4. Data Extraction and Management

A unified method and standard of data extraction were used, in which the two authors (Y.X. and Y.S.) extracted the information in turn, independently. The figures and tables for information would be made after the two authors verified their data finally. An independent arbitrator (D.S.) resolved any discrepancies in data extraction.

The following data are collected. (1) The versions of The Tampa Scale of Kinesiophobia and their test-retest reliabilities, which could be searched in the references of these studies, or be inferred from the nationalities of the participants; (2) The origin scores of the Tampa Scale of Kinesiophobia at baselines and different follow-up times; (3) The mean age of participants which would be combined by statistical Formulas; (4) The types of musculoskeletal pain; (5) The duration of interventions.

All the scores of the Tampa Scale of Kinesiophobia would be converted to the form of MEAN (SD). If an included study reported the Tampa Scale of Kinesiophobia scores of different follow-up times or had more than one trial arm, each different follow-up times and trial arm would be treated as a separate trial [29].

It should be paid attention that some original data of included studies should be revised to unify and standardize. The corrected mean differences and standard deviations of the Tampa Scale of Kinesiophobia scores of the baselines and the follow-up times could be calculated by the basic statistical Formulas (1) and (2) (The number 1 means the baseline and the number 2 represents the follow-ups). The correlation coefficient R was the test-retest reliability or the internal consistency coefficient of the Tampa Scale of Kinesiophobia, which was used in the included studies. Different language versions of the Tampa Scale had different test-retest reliabilities. If a study didn't report the version of the Tampa Scale of Kinesiophobia, the rest-retest reliability would be inferred from the participants' nationalities or references of the study:

$$MD = MD_1 - MD_2, \tag{1}$$

$$SD = \sqrt{SD_1^2 + SD_2^2 - 2R \cdot SD_1 \cdot SD_2},$$
 (2)

Since the scores of the Tampa Scale of Kinesiophobia were in the same units, the standardized mean difference was not chosen to illustrate the pooled effect. The software RevMan5.3 was used to analyze the combined effect, and the random effect model (REM) was chosen. All the total and subtotal results would be shown in the forest plots made by RevMan5.3.

The size of heterogeneity would be tested by two indexes, one of which was I^2 , a qualitative and descriptive index showing the inconsistency of the included studies, and the other was Tau², an quantitative and analytical index showing the true difference. The statistic Q, which was equal to the statistic Chi² calculated by the RevMan5.3, and the confidence intervals of T² and I², could explain whether the result has the true heterogeneity.

The prediction intervals of all the statistics mentioned above, which combines the estimation of the mean effect with the variance of the true effect and approximate the actual dispersion of the true effect as the number of studies tend to infinity, were calculated as well.

2.5. Risk of Bias and Quality of Evidence

A unified assessment method and standard of the risk of bias were used, in which the two authors (Y.X. and Y.S.) assessed each study in turn, independently. The figures for information would be made after the two authors verified their data finally. An independent arbitrator (D.S.) resolved any discrepancies in the assessment of the risk of bias. The Cochrane Collaboration's tool was used to assess the risk of bias [30]. The trials' quality was assessed and graded independently by two authors according to the criteria described in The Cochrane Handbook. And the risk of bias graph and the risk of bias summary graph would be made by RevMan5.3.

A Funnel plot based on the calculation of standard mean difference (SMD) was used in this review to describe the existence of bias across studies. The analysis of bias risk was based on the following model assumptions. (1) Studies with large sample sizes were more likely to be published; (2) Studies on medium-sized samples were easily omitted; (3) Studies with small sample sizes were most likely to be missed.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, which would be made by the software GRADEprofiler (Version 3.2.2), was used to illustrate the quality of evidence [31].

2.6. Addition Analysis

2.6.1. Subgroup Analysis

If the heterogeneity of the pooled effect were large, a subgroup analysis would be necessary to evaluate the source of heterogeneity and the influencing factors of the effect. The heterogeneity between the studies might come from different types of musculoskeletal pain, different follow-up times, and the different mean age of the participants, and different durations of treatments. Therefore, the subgroup analysis would be conducted from the following aspects: (1) Types of musculoskeletal pain; (2) Follow-up times; (3) Mean of the participants; (4) Duration of Treatments; (5) Different control group interventions. All the continuous variables would be divided into several subgroups for analysis. However, the subgroup analysis might not explain the source of heterogeneity. For a certain covariate, a further meta-regression would be made if there were enough studies.

2.6.2. Meta-Regression

Meta-Regression, whose results could explain the correlation of different subgroup deviations and the pooled effect, would be made by the software STATA[®] 14. Following the meta-regression principles, the restricted maximum likelihood (REML) was used in meta-regression, and the regression coefficient is expressed in exponential form (exp). Moreover, the Monte Carlo Method was used to correct the P-value to verify the existence of the type I error. The times of calculation was set to 5000.

2.6.3. Statistical Power

Generally, the statistical power should be analyzed before primary studies or a meta-analysis. However, to verify the rationality of this review's mathematical method, the statistical power of every primary study, meta-analysis, and heterogeneity analysis would be calculated. Generally, although researchers often wanted the statistical power of their study to be at least 80%, a single primary study's statistical power was usually low. The statistical power of studies from medicine, psychology, education, and other fields of science were generally less than 80% and less than 50% when testing for low effects. Since a meta-analysis had a larger sample size than any included study, it usually had higher statistical power. In this review, each included studies' statistical power, the meta-analysis, the subgroup analysis, and the heterogeneity test were calculated.

3. Results

3.1. Study Selection, Information, and Original Data

In the database PubMed, by the search term "(kinesiophobia[Title/Abstract]) AND ((randomized) or (randomised)[Title/Abstract]) NOT ((design) or (protocol)[Title])", and the limitation of "randomized controlled trials", 55 studies had been screened out. In the database Medline (EBSCO), by the search term "AB kinesiophobia and AB (randomized or randomised) NOT TI (design or protocol)", and the range of "Cochrane Central Register of Trials, Medline with Full Text, and CINAHL", 507 studies had been screened out. In the database Ovid, by the search term "(kinesiophobia and (randomized or randomised) .ab not (design or protocol) .at" typed in the tool "Multi-Field Search", and the limitation of English, 480 studies had been screened out. All the results would be downloaded and imported into EndNote X9 for further screening.

After deduplication and applying the exclusion criteria, 12 studies [32–43] of the total 1042 studies were included for analysis. The flow diagram could be seen in Figure 1. Based on the information of all the full texts included, the result of data collection and a summary measure of each included study could be seen in Tables 1 and 2.

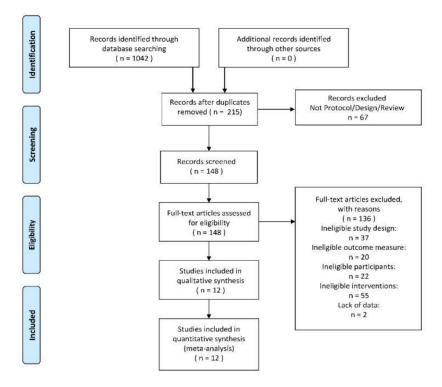


Figure 1. The PRISMA 2009 flow diagram of search and study selection.

				Study Design					Characteris	stics of Participants
G(1	Version	of TSK	Multi-Modal The	erapy Group		Uni-Modal	Therapy Group			
Study	Language R		Intervention	Duration of Intervention (Weeks)	N	Intervention	Duration of Intervention (Weeks)	Ν	Mean Age	Type of Pain
Gardner 2019 [34]	English	0.820	Education + Patient-led goal setting intervention	8	37	Standardised advice to exercise with a plan	8	38	44.51	Chronic Low-back Pian
Nambi 2020-Arm1 [43]	English	0.820	Virtual reality training	4	20	Isokinetic training with a plan	4	20	23.00	Chronic Low-back Pian
Nambi 2020-Arm2	English	0.820	Virtual reality training	4	20	Conventional training with a plan	4	20	23.25	Chronic Low-back Pian
Saracoglu 2020-Arm1 [40]	Turkish	0.806	Manual therapy + Supervised home exercise + Pain neuroscience education	4	20	Manual therapy + Supervised home exercise	4	19	40.50	Chronic Low-back Pian
Saracoglu 2020-Arm2	Turkish	0.806	Manual therapy + Supervised home exercise + Pain neuroscience education	4	20	Supervised home exercise	4	18	39.94	Chronic Low-back Pian
Gustavsson 2006 [32]	Swedish	0.910	Relaxation treatment	7	13	Treatment as usual	20	16	37.48	Chronic Neck Pain
Javdaneh 2020 [42]	Persian	0.920	Cognitive functional therapy + Scapular exercise	6	24	Scapular exercise with a plan	6	24	29.50	Chronic Neck Pain
Ris 2016 [36]	English	0.820	Physical training + Specific exercises + Pain education	16	101	Pain education	16	99	45.15	Chronic Neck Pain
Bahat 2015 [33]	Dutch	0.780	Cervical kinematic training + Interactive Virtual Reality training	5	16	Cervical kinematic training with a plan	5	16	40.88	Chronic Neck Pain
Tompson 2016 [37]	English	0.820	Cognitive-behavioural physiotherapy + Progressive neck exercise	24	29	Progressive neck exercise	24	28	47.53	Chronic Neck Pain
Yilmza 2017 [41]	Turkish	0.806	Virtual walking therapy	2	22	Traditional Physiotherapy	2	22	25.14	Non-special Low-back Pain
Helminen 2015 [39]	Finnish	0.890	Cognitive-behavioral group intervention contains skill training plan	6	55	Ordinary general practitioner care	6	56	63.64	Knee Osteoarthritis Pain
Meijer 2006 [35]	Dutch	0.780	Treatment combined physical and psychological sessions	2	20	Usual care by occupational health services	2	14	38.14	Upper extremity musculoskeletal disorders
Gulsen 2020 [38]	Turkish	0.806	Immersive Virtual Reality + Exercise	8	8	Exercise with a plan	8	8	42.50	Fibromyalgia
Total					405			398		
Average		0.829		7.1			8.1		38.7	

Table 1. The result of data collection.

Study	Group	Baselin	ie (T0)	Foll	ow-Up Times (T1)	Foll	ow-Up Times (T2)	Follow-Up Times (T3)		
Study	Group	TSK +	N ₀	TSK +	Duration	N ₁	TSK +	Duration	N ₂	TSK +	Duration	N_3
Gardner 2019 [34] -	OG	36.60 (7.50)	37	29.30 (6.90)	8	37	30.00 (5.30)	16	37	31.20 (7.90)	48	37
	CG	39.90 (9.30)	38	39.40 (8.30)	8	38	39.30 (8.10)	16	38	37.30 (8.00)	48	38
Nambi 2020-Arm1	OG	57.52 (4.80)	20	26.43 (3.50)	4	20	20.12 (2.50)	24	19			
[43]	CG	58.11 (4.50)	20	27.54 (3.80)	4	20	21.21 (2.40)	24	20			
Nambi 2020-Arm2 -	OG	57.52 (4.80)	20	26.43 (3.50)	4	20	20.12 (2.50)	24	19			
Nambi 2020-Arm2	CG	57.93 (4.30)	20	46.21 (4.10)	4	20	38.64 (3.90)	24	19			
Saracoglu 2020-Arm1	OG	44.35 (4.30)	20	35.55 (5.75)	4	20	35.19 (3.99)	6				
[40]	CG	45.10 (4.45)	19	41.63 (5.23)	4	19	42.21 (5.04)	6				
Saracoglu 2020-Arm2 -	OG	44.35 (4.30)	20	35.55 (5.75)	4	20	35.19 (3.99)	6				
Salacogiu 2020-Affiliz -	CG	45.55 (4.10)	18	44.94 (4.70)	4	18	44.88 (5.10)	6				
Gustavsson 2006 [32] -	OG	26.00 (7.46)	13	27.00 (5.22)	7	13	29.00 (5.22)	20	13			
Gustavsson 2000 [32] -	CG	29.50 (1.67)	16	32.00 (0.00)	7	16	30.00 (2.00)	20	16			
Javdaneh 2020 [42] -	OG	50.00 (5.23)	24	21.00 (5.22)	6	24						
Javuanen 2020 [42] -	CG	49.00 (4.78)	24	30.00 (3.55)	6	24						

 Table 2. The converted scores of TSK by the form of MEAN (SD).

C	Carrier	Baselin	ie (T0)	Fol	low-Up Times (T1)	Fol	low-Up Times (T2)	Follow-Up Times (T3)		
Study	Group	TSK +	N ₀	TSK +	Duration	N1	TSK +	Duration	N_2	TSK +	Duration	N ₃
Ris 2016 [36]	OG	37.80 (0.69)	101	36.57 (4.50)	16	101						
KIS 2016 [56]	CG	37.70 (0.71)	99	37.49 (4.50)	16	99						
Bahat 2015 [33]	OG	32.75 (6.80)	16	30.13 (5.70)	5	16	31.23 (6.50)	12	14			
Dallat 2013 [33]	CG	30.38 (5.80)	16	28.64 (9.90)	5	14	30.00 (5.90)	12	12			
Tompson 2016 [37]	OG	36.70 (7.10)	29	32.00 (14.11)	24	29						
10111pson 2010 [07]	CG	33.60 (9.00)	28	33.80 (15.04)	24	28						
Yilmza 2017 [41]	OG	43.72 (4.32)	22	29.56 (4.04)	2	22						
	CG	40.36 (5.61)	22	38.70 (5.44)	2	22						
Helminen 2015 [39]	OG	35.00 (1.25)	55	33.00 (1.05)	6	55						
	CG	33.30 (1.35)	56	32.50 (1.33)	6	56						
Meijer 2006 [35]	OG	38.90 (1.51)	20	29.10 (1.54)	8	20	25.80 (2.65)	24	20	26.40 (1.90)	48	20
weger 2000 [55]	CG	40.91 (1.81)	14	41.00 (1.68)	8	14	39.90 (3.16)	24	14	40.40 (2.65)	48	14
Gulsen 2020 [38]	OG	49.00 (4.44)	8	35.00 (7.41)	8	8						
Guiscii 2020 [30]	CG	47.00 (7.22)	8	40.00 (5.37)	8	8						

Table 2. Cont.

+: Mean (SD); TSK: Tampa scale of Kinesiophobia; OG: Operate group (Multi-modal therapy); CG: Control group (Uni-modal therapy).

3.2. Risk of Bias

The result of the criteria for judging the risk of bias in the "Risk of bias assessment tool" would be shown in Figure 2a,b. A funnel plot of the included studies, as in Figure 2c, illustrated the risk of bias across studies and showed the relationship between the sample size and the effect. And the result of the assessment of evidence quality, which was made by following the GRADE, would be put into the Supplementary File (Figure S1).

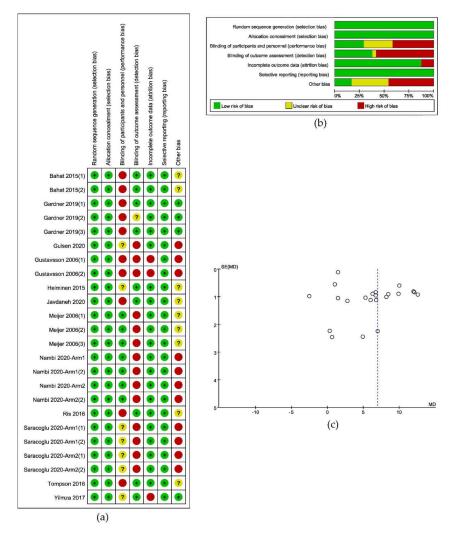


Figure 2. Results of risk of bias analysis: (**a**) Risk of bias summary; (**b**) Graph of risk of bias; (**c**) Funnel plot of included studies.

3.3. Data Extraction and Management

In the comparison of multi-modal interventions and uni-modal interventions with the scores of TSK as the outcome, all the 12 included studies were divided into 24 independent trials. The result of original data processing was shown in Table 3, and the forest plots of the pooled effect, which were calculated by RevMan5.3, were shown in Figure 3.

C11	Duration of	Follow-Uj	^p Mean	E	xperimer	nt		Control	
Study	Intervention (Weeks)	Times (Weeks)	Age	MD	SD	Ν	MD	SD	Ν
Gardner 2019 (1) [34]	8	8	44.51	7.30	4.36	37	0.50	5.37	38
Gardner 2019 (2)	8	16	44.51	6.60	4.38	37	0.60	5.34	38
Gardner 2019 (3)	8	48	44.51	5.40	4.64	37	2.60	5.34	38
Nambi 2020-Arm1 (1) [43]	4	4	23.00	31.09	2.78	20	24.34	2.58	20
Nambi 2020-Arm1 (2)	4	24	23.00	37.40	3.18	20	30.67	2.88	20
Nambi 2020-Arm2 (1)	4	4	23.25	31.09	2.78	20	11.72	2.53	20
Nambi 2020-Arm2 (2)	4	24	23.25	37.40	3.18	20	19.29	2.63	20
Saracoglu 2020-Arm1 (1) [40]	4	4	40.50	8.80	3.42	20	3.47	3.10	19
Saracoglu 2020-Arm1 (2)	4	6	40.50	9.16	2.60	20	2.89	3.01	19
Saracoglu 2020-Arm2 (1)	4	4	39.94	8.80	3.42	20	0.61	2.78	18
Saracoglu 2020-Arm2 (2)	4	6	39.94	9.16	2.60	20	0.67	3.02	18
Gustavsson 2006 (1) [32]	7	7	37.48	-1.00	3.47	13	-2.50	1.67	16
Gustavsson 2006 (2)	7	20	37.48	-3.00	3.47	13	-0.50	0.84	16
Javdaneh 2020 [42]	6	6	29.50	29.00	2.09	24	19.00	2.06	24
Ris 2016 [36]	16	16	45.15	1.23	3.95	101	0.21	3.93	99
Bahat 2015 (1) [33]	5	5	40.88	2.13	4.20	16	1.50	8.30	14
Bahat 2015 (2)	5	12	40.88	1.23	6.80	14	0.92	4.50	12
Tompson 2016 [37]	24	24	47.53	4.70	9.23	29	-0.20	9.23	28
Yilmza 2017 [41]	2	2	25.14	14.26	2.62	22	1.66	3.45	22
Helminen 2015 [39]	6	6	63.64	2.00	0.57	55	0.50	0.63	56
Meijer 2006 (1) [35]	2	8	38.14	9.80	1.01	20	-0.10	3.26	14
Meijer 2006 (2)	2	24	38.14	13.10	1.75	20	1.00	2.77	14
Meijer 2006 (3)	2	48	38.14	12.50	1.20	20	0.50	2.86	14
Gulsen 2020 [38]	8	8	42.50	14.00	4.65	8	7.00	4.30	8

Table 3. The result of original data processing.

MD: Mean Difference; SD: Standard Deviation; N: Sample Size.

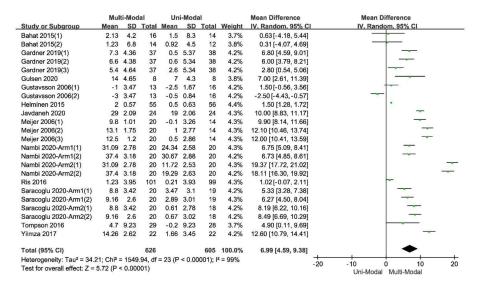


Figure 3. The forest plot of the comparison between the multi-modal therapies and uni-modal therapies.

The Q statistic of the meta-analysis of all included studies (equal to Chi²), T², I² and their 95% confidence intervals and prediction intervals of the comparisons' effect could be seen in Table 4.

Stat	Statistics of Heterogeneity Test				I of T ²	95% C	CI of I ²	Prediction Intervals		
df	Q	I ²	Tau ²	LL	UL	LL	UL	LL	UL	
23	1549.94	99%	34.21	3.37	4.09	0.87	0.89	0.00 *	19.33	

Table 4. The result of heterogeneity test of all included studies.

df: Degree of freedom; LL: Lower limit; UL: Upper limit; *: the true value is less than 0.

3.4. Additional Analysis

3.4.1. Subgroup Analysis

The calculation of subgroup analysis was based on the randomized effect model by RevMan5.3. According to the result of the subgroup analysis, there was a large heterogeneity within studies in subgroup analysis since the I^2 of each subgroup analysis was large, meaning that the different subgroups may not be the sources of the heterogeneity within the included studies, and it was necessary to do a meta-regression.

According to the characteristics of participants and design of the included studies which might affect the effectiveness of therapies, there were five subdivisions in the subgroup analysis: (1) different types of pain, which included chronic low-back pain, chronic neck pain, and non-special low-back pain; (2) different ranges of participants' mean age which included 20 to 30, 30 to 40, and more than 40 years old; (3) different durations of treatments which included 0 to 3 weeks, 4 to 6 weeks, 7 to 9 weeks and more than 9 weeks; (4) different follow-up times which included 0 to 12 weeks, 13 to 24 weeks and more than 24 weeks; (5) different types of uni-modal interventions in control groups, which include passive physical therapy, active exercise, and only psychological education (following the hypothesis that there were different effects between passive physical therapies, active exercise, and psychological-only interventions). The indexes of heterogeneity and their 95% confidence intervals were shown in Table 5, and all the forest plots of the subdivisions would be shown in Figure 4.

		ti-Mod			i-Moda			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	\$D	Total	Weight	IV, Random, 95% C	IV, Random, 95% CI
1.1.1 Chronic Low-back F	Pian								
Gardner 2019(1)	7.3	4.36	37	0.5	5.37	38	4.2%	6.80 [4.59, 9.01]	
Gardner 2019(2)	6.6	4.38	37	0.6	5.34	38	4.2%	6.00 [3.79, 8.21]	
Gardner 2019(3)	5.4	4.64	37	26	5.34	38	4.2%	2.80 [0.54, 5.06]	
Nambi 2020-Arm1(1)	31.09		20	24.34		20	4.3%	6.75 [5.09, 8.41]	
ambi 2020-Arm1(2)	37.4	3.18	20	30.67	2.88	20	4.2%	6.73 [4.85, 8.61]	
	31.09		20	11.72		20	4.3%		
Nambi 2020-Arm2(1)								19.37 [17.72, 21.02]	
Nambi 2020-Arm2(2)	37.4	3.18	20	19.29	2.63	20	4.2%	18.11 [16.30, 19.92]	
Saracoglu 2020-Arm1(1)		3.42	20	3.47	3.1	19	4.2%	5.33 [3.28, 7.38]	
Saracoglu 2020-Arm1(2)	9.16	2.6	20	2.89		19	4.3%	6.27 [4.50, 8.04]	
Saracoglu 2020-Arm2(1)	8.8	3.42	20	0.61	2.78	18	4.2%	8.19 [6.22, 10.16]	
Saracoglu 2020-Arm2(2)	9.16	2.6	20	0.67	3.02	18	4.2%	8.49 [6.69, 10.29]	
Subtotal (95% CI)			271			268	46.5%	8.64 [5.37, 11.91]	
Heterogeneity: Tau ² = 29.6	2: Chi2 :	= 323.8	0. df =	10 (P -	: 0.000	01): P	= 97%		
est for overall effect: Z =				(,, .			
.1.2 Chronic Neck Pain									
Bahat 2015(1)	2.13	4.2	16	1.5	8.3	14	3.7%	0.63 [-4.18, 5.44]	
Bahat 2015(2)	1.23	6.8	14	0.92	4.5	12	3.8%	0.31 [-4.07, 4.69]	
Sustavsson 2006(1)	-1	3.47	13		1.67	16	4.2%	1.50 [-0.56, 3.56]	
Sustavsson 2006(2)	-3	3.47	13		0.84	16	4.2%	-2.50[-4.43,-0.57]	
lavdaneh 2020	29	2.09	24	19		24	4.3%	10.00 [8.83, 11.17]	
Ris 2016	1.23	3.95	101	0.21		99	4.3%	1.02[-0.07, 2.11]	
Compson 2016	4.7	9.23	29	-0.2	9.23	28	3.7%	4.90 [0.11, 9.69]	
Subtotal (95% CI)			210			209	28.3%	2.30 [-1.85, 6.45]	
1.1.3 Non-special Low-ba	ck Pain	8							
	14.26		22	1.66	3.45	22	4.2%	12.60 [10.79, 14.41]	T
Subtotal (95% CI)	14.26		22 22	1.66	3.45	22 22	4.2% 4.2%	12.60 [10.79, 14.41] 12.60 [10.79, 14.41]	Ŧ
Subtotal (95% CI) Heterogeneity: Not applica	14.26 ble	2.62	22	1.66	3.45				•
Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z =	14.26 ble 13.64 (P	2.62	22	1.66	3.45				•
Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 1.1.4 Knee Osteoarthritis	14.26 ble 13.64 (P Pain	2.62	22 0001)			22	4.2%	12.60 [10.79, 14.41]	•
Yilmza 2017 Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 1.1.4 Knee Osteoarthritis Heiminen 2015 Subtotal (95% CI)	14.26 ble 13.64 (P Pain	2.62	22 1001) 55		3.45 0.63	22 56	4.2% 4.4%	12.60 [10.79, 14.41] 1.50 [1.28, 1.72]	•
Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 1.1.4 Knee Osteoarthritis Helminen 2015 Subtotal (95% CI)	14.26 ble 13.64 (P Pain 2	2.62	22 0001)			22	4.2%	12.60 [10.79, 14.41]	Ŧ
Subtotal (95% CI) Heterogeneity: Not applica Fest for overall effect: Z = 1.1.4 Knee Osteoarthritis Helminen 2015 Subtotal (95% CI) Heterogeneity: Not applica	14.26 ble 13.64 (P Pain 2 ble	2.62 < 0.00 0.57	22 0001) 55 55			22 56	4.2% 4.4%	12.60 [10.79, 14.41] 1.50 [1.28, 1.72]	Ŧ
Subtotal (95% CI) Heterogeneity: Not applica Fest for overall effect: Z = 1.1.4 Knee Osteoarthritis Helminen 2015 Subtotal (95% CI) Heterogeneity: Not applica Fest for overall effect: Z =	14.26 ble 13.64 (P Pain 2 ble 13.16 (P	2.62 < 0.00 0.57	22 1001) 55 55 1001)	0.5		22 56	4.2% 4.4%	12.60 [10.79, 14.41] 1.50 [1.28, 1.72]	Ŧ
Subtotal (95% Cl) Heterogeneity: Not applica Test for overall effect: Z = ' 1.1.4. Knee Osteoarthritis Heiminen 2015 Subtotal (95% Cl) Heterogeneity: Not applica Test for overall effect: Z = ' 1.1.5. Upper extremity mu	14.26 ble 13.64 (P Pain 2 ble 13.16 (P ssculos)	2.62 < 0.00 0.57 < 0.00 celetal	22 1001) 55 55 1001) disord	0.5 Iers	0.63	22 56 56	4.2% 4.4% 4.4%	12.60 (10.79, 14.41) 1.50 [1.28, 1.72] 1.50 [1.28, 1.72]	Ť
Subtotal (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 1.1.4 Knee Osteoarthritis Helenogeneity: Not applica Test for overall effect: Z = 1.1.5 Upper extremity mu Weijer 2006(1)	14.26 ble 13.64 (P Pain 2 ble 13.16 (P 13.16 (P 9.8	2.62 < 0.00 0.57 < 0.00 seletal 1.01	22 0001) 55 55 0001) disord 20	0.5 ers -0.1	0.63	22 56 56	4.2% 4.4% 4.4% 4.3%	12.60 (10.79, 14.41) 1.50 (1.28, 1.72) 1.50 (1.28, 1.72) 9.90 (8.14, 11.66)	•
Subtotal (95% CI) Hetersgeneity: Not applica fest for overall effect: Z = 1.1.4 Knee Osteoarthritis Herminen 2015 Subtotal (95% CI) Hetersgeneity: Not applica fest for overall effect: Z = 1.1.5 Upper extremity mu doijer 2006(1) doijer 2006(2)	14.26 ble 13.64 (P Pain 2 ble 13.16 (P sculos) 9.8 13.1	2.62 - < 0.00 0.57 - < 0.00 seletal 1.01 1.75	22 0001) 55 55 0001) disord 20 20	0.5 Iers -0.1 1	0.63 3.26 2.77	22 56 56 14 14	4.2% 4.4% 4.4% 4.3% 4.3%	12.60 (10.79, 14.41) 1.50 [1.28, 1.72] 1.50 [1.28, 1.72] 9.90 [8.14, 11.66] 12.10 [10.46, 13.74]	÷
Subtotal (65% CI) Heterogeneity: Not applica Test for overall effect: Z = 1.1.4 Knee Osteoarthritis Helminen 2015 Subtotal (65% CI) Heterogeneity: Not applica Test for overall effect: Z = 1.1.5 Upper extremity mu Weijer 2006(2) Weijer 2006(2)	14.26 ble 13.64 (P Pain 2 ble 13.16 (P 13.16 (P 9.8	2.62 < 0.00 0.57 < 0.00 seletal 1.01	22 0001) 55 55 0001) disord 20 20 20	0.5 Iers -0.1 1	0.63	22 56 56 14 14 14	4.2% 4.4% 4.4% 4.3% 4.3% 4.3%	12.60 (10.79, 14.41) 1.50 [1.28, 1.72] 1.50 [1.28, 1.72] 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59]	
Subtotal (65% CI) eleforganely: KN applica Fest for overall effect: Z = 1.1.4 Knee Osteoarthritis teminen 2015 telatosanoly: Not applica subtotal (95% CI) telatoganoly: Not applica fest for overall effect: Z = 1.1.5 Upper extremity mu deijer 2006(1) deijer 2006(2) deijer 2006(2) deijer 2006(3) Subtotal (95% CI)	14.26 ble 13.64 (P Pain 2 ble 13.16 (P isculosi 9.8 13.1 12.5	2.62 - < 0.00 0.57 - < 0.00 seletal 1.01 1.75 1.2	22 0001) 55 55 0001) disord 20 20 20 60	0.5 ers -0.1 1 0.5	0.63 3.26 2.77 2.86	22 56 56 14 14 14 14	4.2% 4.4% 4.4% 4.3% 4.3%	12.60 (10.79, 14.41) 1.50 [1.28, 1.72] 1.50 [1.28, 1.72] 9.90 [8.14, 11.66] 12.10 [10.46, 13.74]	- - -
Subtotal (95% C)) Heterogeneily: No: applica set for overall effect: Z = 1.1.4 Knee Osteoarthritis Heiminen 2015 Subtotal (95% C)) Heterogeneily: No: applica rest for overall effect: Z = 1.1.5 Upper activenity mu Aeijer 2006(2) Aeijer 2006(2) Aeijer 2006(2) Subtotal (95% C)] Heterogeneily: Tau ² = 0.73	14.26 ble Pain 2 ble 13.16 (P isculos) 9.8 13.1 12.5 3; Chi ² =	2.62 - < 0.00 0.57 - < 0.00 celetal 1.01 1.75 1.2 4.02, d	22 0001) 55 55 0001) disord 20 20 60 0ff = 2 (f	0.5 ers -0.1 1 0.5	0.63 3.26 2.77 2.86	22 56 56 14 14 14 14	4.2% 4.4% 4.4% 4.3% 4.3% 4.3%	12.60 (10.79, 14.41) 1.50 [1.28, 1.72] 1.50 [1.28, 1.72] 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59]	
Subtotal (95% CI) Heterogeneity: No: applica test for overall effect: Z = 1.1.4 Knee Osteoarthritis Heterogeneity: No: applica Test for overall effect: Z Holy 2006(1) Moijer 2006(2) Moijer 2006(2) Subtotal (95% CI) Heterogeneity: Tau" = 0.73 Test for overall effect: Z =	14.26 ble Pain 2 ble 13.16 (P isculos) 9.8 13.1 12.5 3; Chi ² =	2.62 - < 0.00 0.57 - < 0.00 celetal 1.01 1.75 1.2 4.02, d	22 0001) 55 55 0001) disord 20 20 60 0ff = 2 (f	0.5 ers -0.1 1 0.5	0.63 3.26 2.77 2.86	22 56 56 14 14 14 14	4.2% 4.4% 4.4% 4.3% 4.3% 4.3%	12.60 (10.79, 14.41) 1.50 [1.28, 1.72] 1.50 [1.28, 1.72] 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59]	
Subtotal (05% CI) eleforganely: Not applica Fest for overall effect: Z = 1.1.4 Knee Osteoarthritis Heimiana 2016 Heimiana 2016 H	14.26 ble 13.64 (P Pain 2 ble 13.16 (P isculos) 9.8 13.1 12.5 3; Chi ² = 16.37 (P	2.62 < 0.00 0.57 < 0.00 celetal 1.01 1.75 1.2 4.02, d < 0.00	22 1001) 55 55 1001) disord 20 20 60 1f = 2 (f	0.5 -0.1 1 0.5 P = 0.13	0.63 3.26 2.77 2.86 3); I ² =	22 56 56 14 14 14 42 50%	4.2% 4.4% 4.4% 4.3% 4.3% 4.3% 12.8%	12.60 (10.79, 14.41) 1.50 (1.28, 1.72) 1.50 (1.28, 1.72) 9.90 (8.14, 11.86) 12.10 (10.46, 13.74) 12.00 (10.41, 13.69) 11.37 (10.01, 12.74)	
Subtola (85% CI) Heterogeneity: Not applica Test for overall effect: Z = 11.1.4 Knee Ostaoarthritis Heterogeneity: Not applica Subtola (85% CI) Heterogeneity: Not applica Test for overall effect: Z = 11.5 Upper extremity mu Weijer 2006(3) Weijer 2006(3) Weijer 2006(3) Subtolal (85% CI) Heterogeneity: Tau ² = 0.73 Test for overall effect: Z = 1.1.6 Fibromyalgia Sulsen 2020	14.26 ble 13.64 (P Pain 2 ble 13.16 (P isculos) 9.8 13.1 12.5 3; Chi ² = 16.37 (P	2.62 - < 0.00 0.57 - < 0.00 celetal 1.01 1.75 1.2 4.02, d	22 0001) 55 55 0001) disord 20 20 20 20 60 1f = 2 (f 0001) 8	0.5 ers -0.1 1 0.5	0.63 3.26 2.77 2.86	22 56 56 14 14 14 42 50% 8	4.2% 4.4% 4.4% 4.3% 4.3% 12.8% 3.8%	12.60 (10.79, 14.41) 1.50 (1.28, 1.72] 1.50 (1.28, 1.72] 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.20 [10.41, 13.69] 11.37 [10.01, 12.74] 7.00 [2.61, 11.39]	
Subtotal (95% CI) Heteroganely: Not spplica Test for overall effect: Z = 1.1.4 Knee Ostaoarthritis Hetminen 2015 Subtotal (95% CI) Heteroganely: Not spplica Test for overall offect: Z = 1.1.5 Upper extremity mu Weijer 2006(3) Weijer 2006(3) Subtotal (95% CI) Heteroganely: Tau ² = 0.73 Test for overall effect: Z = 1.1.6 Fibromyalgia Subtota (95% CI) Heteroganely: Not applica	14.26 ble Pain 2 ble 13.16 (P isculos) 9.8 13.11 12.5 3; Chi ² = 16.37 (P 14 ble	2.62 < 0.00 0.57 < 0.00 xeletal 1.01 1.75 1.2 4.02, d < 0.00 4.65	22 0001) 55 55 0001) disord 20 20 20 60 0 ff = 2 (f 0001) 8 8 8	0.5 -0.1 1 0.5 P = 0.13	0.63 3.26 2.77 2.86 3); I ² =	22 56 56 14 14 14 42 50%	4.2% 4.4% 4.4% 4.3% 4.3% 4.3% 12.8%	12.60 (10.79, 14.41) 1.50 (1.28, 1.72) 1.50 (1.28, 1.72) 9.90 (8.14, 11.86) 12.10 (10.46, 13.74) 12.00 (10.41, 13.69) 11.37 (10.01, 12.74)	
Subtota (65% CI) Heteroganely: Not spolica Test for overall effect: Z = 1.1.4 Knee Ostaoarthritis Hetminen 2015 Subtota (65% CI) Heteroganely: Not spolica Test for overall offect: Z = 1.1.5 Upper extremity mu Weijer 2006(1) Weijer 2006(2) Weijer 2006(2) Weijer 2006(2) Heteroganely: Tau ⁺ = 0.7 Test for overall offect: Z = 1.1.5 Fibrorwalgia Subtota (65% CI) Heteroganely: Not applica Test for overall offect: Z =	14.26 ble Pain 2 ble 13.16 (P isculos) 9.8 13.11 12.5 3; Chi ² = 16.37 (P 14 ble	2.62 < 0.00 0.57 < 0.00 xeletal 1.01 1.75 1.2 4.02, d < 0.00 4.65	22 0001) 55 55 0001) disord 20 20 20 60 ff = 2 (f 0001) 8 8 8	0.5 -0.1 1 0.5 P = 0.13	0.63 3.26 2.77 2.86 3); I ² =	22 56 56 56 14 14 14 42 50% 8 8 8	4.2% 4.4% 4.3% 4.3% 4.3% 12.8% 3.8% 3.8%	12.60 (10.79, 14.41) 1.50 (1.28, 1.72] 1.50 (1.28, 1.72] 1.50 (1.28, 1.72] 1.10 (10.46, 13.74] 12.00 (10.41, 13.69] 11.37 (10.01, 12.74] 7.00 [2.61, 11.39]	
Subtota (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 1.1.4 Knee Osteoarthritis Heiminan 2015 Subtota (95% CI) Heterogeneity: Not applica Test for overall effect: Z = 1.1.5 Upper extremity mu Weijer 2006(1) Weijer 2006(2) Weijer 2006(2) Subtota (95% CI) Heterogeneity: Tau'' = 0.73 Subtota (95% CI) Heterogeneity: Not applica Test for overall effect: Z = : Total (95% CI)	14.26 ble 13.64 (P Pain 2 ble 13.16 (P sculos) 9.8 13.16 (P sculos) 9.8 13.1 12.5 5; ChP = = 16.37 (P 14 ble 3.13 (P :	2.62 < 0.00 0.57 < 0.00 celetal 1.01 1.75 1.2 4.02, d 4.02, d 4.65 = 0.002	22 0001) 55 55 0001) disord 20 20 20 60 60 60 60 60 60 8 8 8 8 8 8 8	0.5 -0.1 1 0.5 2 = 0.13 7	0.63 3.26 2.77 2.86 3); F = 4.3	22 56 56 56 14 14 42 50% 8 8 8 8	4.2% 4.4% 4.3% 4.3% 12.8% 3.8% 3.8% 3.8%	12.60 (10.79, 14.41) 1.50 (1.28, 1.72] 1.50 (1.28, 1.72] 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.20 [10.41, 13.69] 11.37 [10.01, 12.74] 7.00 [2.61, 11.39]	
Subtota (65% CI) Heteroganely: Not spolica Test for overall effect: Z = 1.1.4 Knee Ostaoarthritis Hetminen 2015 Subtota (65% CI) Heteroganely: Not spolica Test for overall offect: Z = 1.1.5 Upper extremity mu Weijer 2006(1) Weijer 2006(2) Weijer 2006(2) Weijer 2006(2) Heteroganely: Tau ⁺ = 0.7 Test for overall offect: Z = 1.1.5 Fibrorwalgia Subtota (65% CI) Heteroganely: Not applica Test for overall offect: Z =	14.26 ble 13.64 (P Pain 2 ble 13.16 (P sculos) 9.8 13.16 (P sculos) 9.8 13.1 12.5 5; ChP = = 16.37 (P 14 ble 3.13 (P :	2.62 < 0.00 0.57 < 0.00 celetal 1.01 1.75 1.2 4.02, d 4.02, d 4.65 = 0.002	22 0001) 55 55 0001) disord 20 20 20 60 60 60 60 60 60 8 8 8 8 8 8 8	0.5 -0.1 1 0.5 2 = 0.13 7	0.63 3.26 2.77 2.86 3); F = 4.3	22 56 56 56 14 14 42 50% 8 8 8 8	4.2% 4.4% 4.3% 4.3% 12.8% 3.8% 3.8% 3.8%	12.60 (10.79, 14.41) 1.50 (1.28, 1.72] 1.50 (1.28, 1.72] 1.50 (1.28, 1.72] 1.10 (10.46, 13.74] 12.00 (10.41, 13.69] 11.37 (10.01, 12.74] 7.00 [2.61, 11.39]	



Figure 4. Cont.

tudy or Subgroup	Multi Mean	-Modal SD To		Uni Mean	i-Moda SD		Weight	Mean Difference IV. Random. 95% Cl	Mean Difference IV. Random. 95% Cl
.4.1 20-30									
avdaneh 2020	29		24		2.06	24	4.7%	10.00 [8.83, 11.17]	-
ambi 2020-Arm1(1)	31.09			24.34	2.58	20	4.6%	6.75 [5.09, 8.41]	
ambi 2020-Arm1(2)		3.18		30.67	2.88	20	4.6%	6.73 [4.85, 8.61]	-
ambi 2020-Arm2(1)	31.09			11.72	2.53	20	4.6%	19.37 [17.72, 21.02]	
ambi 2020-Arm2(2)		3.18		19.29	2.63	20	4.6%	18.11 [16.30, 19.92]	
imza 2017 ubtotal (95% CI)	14.26		22 126	1.66	3.45	22 126	4.6%	12.60 [10.79, 14.41] 12.26 [8.06, 16.46]	-
eterogeneity: Tau ² = 26.84	A. Chil -				0000			12.20 [0.00, 10.40]	
est for overall effect: Z = 5	5.72 (P <	0.00001	1)	5 (P < 1	0.0000	1), 1	9070		
4.2 30-40									
ustavsson 2006(1)	-1	3 47	13	-25	1.67	16	4 6%	1.50 [-0.56, 3.56]	
ustavsson 2006(2)		3.47	13		0.84	16	4.6%	-2.50 [-4.43, -0.57]	
leijer 2006(1)	9.8	1.01	20	-0.1	3.26	14	4.6%	9.90 [8.14, 11.66]	
leijer 2006(2)	13.1	1.75	20	1	2.77	14	4.6%	12.10 [10.46, 13.74]	
leijer 2006(3)	12.5	1.2	20		2.86	14	4.6%	12.00 [10.41, 13.59]	-
aracoglu 2020-Arm2(1)	8.8		20	0.61	2.78	18	4.6%	8.19 [6.22, 10.16]	
aracoglu 2020-Arm2(2)	9.16	2.6	20	0.67	3.02	18	4.6%	8.49 [6.69, 10.29]	
ubtotal (95% CI)			126			110	32.3%	7.12 [3.13, 11.11]	-
eterogeneity: Tau ² = 28.12 est for overall effect: Z = 3	2; Chi ² = 3 50 (P =	204.81, 0.0005)	df = 6	6 (P < 0	0.0000	1); ² =	97%		
	0100 (1	0.0000)							
.4.3 40+ ahat 2015(1)	2.13	4.2	16	1.5	8.3	14	4.1%	0.63[.4.40 5.44	
Sahat 2015(1) Sahat 2015(2)	2.13	4.2 6.8	16 14	1.5	8.3	14	4.1%	0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69]	
anat 2015(2) Sardner 2019(1)	7.3		14 37		4.5 5.37	38	4.2%	6.80 [4.59, 9.01]	
Sardner 2019(1)	6.6	4.30	37	0.6	5.34	38	4.6%	6.00 [3.79, 8.21]	
Gardner 2019(3)	5.4	4.64	37	2.6	5.34	38	4.6%	2.80 [0.54, 5.06]	
lelminen 2015	2	0.57	55	0.5	0.63	56	4.7%	1.50 [1.28, 1.72]	
Saracoglu 2020-Arm1(1)	8.8	3.42	20	3.47	3.1	19	4.6%	5.33 [3.28, 7.38]	
Saracoglu 2020-Arm1(2)	9.16	2.6	20		3.01	19	4.6%	6.27 [4.50, 8.04]	
ompson 2016	4.7	9.23	29		9.23	28	4.1%	4.90 [0.11, 9.69]	-
Subtotal (95% CI)		2	265			262	39.9%	4.03 [2.03, 6.04]	•
leterogeneity: Tau ² = 7.36; est for overall effect: Z = 3	; Chi² = 7	8.96, df	= 8 (P < 0.0	10001);	l ² = 90	1%		
	0.04 (F <								-
otal (95% CI)			517			498	100.0%	7.26 [4.62, 9.89]	
leterogeneity: Tau ² = 38.44	4; Chi ² =	1532.59	9, df =	21 (P	< 0.00	001); l ^a	= 99%		-20 -10 0 10
est for overall effect: Z = 5 est for subgroup difference	5.39 (P <	0.00001	1)	0 /0 - /	0.000	12 - 04	00/		Uni-Modal Multi-Modal
est for subaroup difference	es: Chi ² =	= 12.47.	df = 2	2(P = (0.0021.	1 ^z = 84	.0%		
							(1-)		
							(b)	,	
	Mult	i-Modal			i-Moda		. ,	Mean Difference	Mean Difference
Study or Subgroup	Mult Mean	ti-Modal SD T					(D) Weight	Mean Difference	Mean Difference IV. Random, 95% Cl
1.6.1 0-3 weeks	Mean	SD T	otal	Меап	SD	Total	Weight	Mean Difference IV, Random, 95% CI	
1.6.1 0-3 weeks Meijer 2006(1)	Mean 9.8	SD T	Total 20	<u>Меап</u> -0.1	SD 3.26	Total	Weight 4.3%	Mean Difference IV, Random, 95% CI 9.90 [8.14, 11.66]	
1.6.1 0-3 weeks Meijer 2006(1) Meijer 2006(2)	Mean 9.8 13.1	SD T 1.01 1.75	20 20	Mean -0.1 1	SD 3.26 2.77	Total 14 14	Weight 4.3% 4.3%	Mean Difference IV, Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74]	
1.6.1 0-3 weeks Meijer 2006(1) Meijer 2006(2) Meijer 2006(3)	9.8 13.1 12.5	SD T 1.01 1.75 1.2	20 20 20 20	-0.1 1 0.5	SD 3.26 2.77 2.86	Total 14 14 14	Weight 4.3% 4.3% 4.3%	Mean Difference IV, Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59]	
1.6.1 0-3 weeks Meijer 2006(1) Meijer 2006(2) Meijer 2006(3) Yilmza 2017	Mean 9.8 13.1	SD T 1.01 1.75 1.2	20 20 20 20 22	Mean -0.1 1	SD 3.26 2.77 2.86	Total 14 14 14 22	Weight 4.3% 4.3% 4.3% 4.2%	Mean Difference IV, Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.60 [10.79, 14.41]	
1.6.1 0-3 weeks Meijer 2006(1) Meijer 2006(2) Meijer 2006(3) Yilmza 2017 Subtotal (95% CI)	9.8 13.1 12.5 14.26	SD T 1.01 1.75 1.2 2.62	20 20 20 22 82	-0.1 1 0.5 1.66	3.26 2.77 2.86 3.45	Total 14 14 14 22 64	Weight 4.3% 4.3% 4.3%	Mean Difference IV, Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59]	
1.6.1 0-3 weeks Meijer 2006(1) Meijer 2006(2) Meijer 2006(3) Yilmza 2017	9.8 13.1 12.5 14.26 8; Chi ² = 5	SD T 1.01 1.75 1.2 2.62 5.31, df =	20 20 20 22 82 = 3 (P	-0.1 1 0.5 1.66	3.26 2.77 2.86 3.45	Total 14 14 14 22 64	Weight 4.3% 4.3% 4.3% 4.2%	Mean Difference IV, Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.60 [10.79, 14.41]	
1.6.1 0-3 weeks Meijer 2006(1) Meijer 2006(2) Meijer 2006(3) Yilmza 2017 Subtotal (95% Cl) Heterogeneity: Tau ² = 0.58 Test for overall effect: Z = 1	9.8 13.1 12.5 14.26 8; Chi ² = 5	SD T 1.01 1.75 1.2 2.62 5.31, df =	20 20 20 22 82 = 3 (P	-0.1 1 0.5 1.66	3.26 2.77 2.86 3.45	Total 14 14 14 22 64	Weight 4.3% 4.3% 4.3% 4.2%	Mean Difference IV, Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.60 [10.79, 14.41]	
1.6.1 0-3 weeks Meijer 2006(1) Meijer 2006(2) Meijer 2006(3) Yilmza 2017 Subtotal (95% Cl) Heterogeneity: Tau ² = 0.58 Test for overall effect: Z = 1 1.6.2 4-6 weeks	9.8 13.1 12.5 14.26 8; Chi ² = 5 20.24 (P	SD T 1.01 1.75 1.2 2.62 5.31, df = < 0.0000	20 20 20 22 82 = 3 (P 01)	-0.1 1 0.5 1.66	3.26 2.77 2.86 3.45 5); I ² =	Total 14 14 14 22 64 44%	Weight 4.3% 4.3% 4.3% 4.2% 17.0%	Mean Difference IV. Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.46, 13.74] 12.60 [10.79, 14.41] 11.66 [10.53, 12.79]	
1.6.1 0.3 weeks Meijer 2006(2) Meijer 2006(2) Yilmza 2017 Subtotal (95% CI) Heterogeneity: Tau ² = 0.58 Test for overall effect: Z = : 1.6.2 4-6 weeks Bahat 2015(1)	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 1 20.24 (P 2.13	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2	20 20 20 22 82 = 3 (P 01)	Mean -0.1 1 0.5 1.66 P = 0.15 1.5	3.26 2.77 2.86 3.45 5); I ² = 8.3	Total 14 14 14 22 64 44%	Weight 4.3% 4.3% 4.3% 4.2% 17.0% 3.7%	Mean Difference IV, Random, 95% CI 9.50 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.60 [10.79, 14.41] 11.66 [10.53, 12.79] 0.63 [-4.18, 5.44]	
1.6.1 0.3 weeks Meijer 2006(1) Meijer 2006(2) Meijer 2006(3) Yilmza 2017 Subtotal (95% CI) Heterogeneity: Tau ² = 0.58 Test for overall effect: Z = 1 1.6.2 4-6 weeks Bahat 2015(2) Bahat 2015(2)	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 1 20.24 (P 2.13 1.23	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2 6.8	20 20 20 22 82 = 3 (P 01)	Mean -0.1 1 0.5 1.66 9 = 0.15 1.5 0.92	3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63	Total 14 14 14 22 64 44%	Weight 4.3% 4.3% 4.3% 4.2% 17.0% 3.7% 3.8%	Mean Difference IV, Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.56] 12.66 [10.79, 14.41] 11.66 [10.53, 12.79] 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(3) Yimra 2017 Subtotal (95% C1) Heterogeneity: Tara's 0.58 Test for overall offect: Z = : 1.5.2 4-5 weeks Bahat 2015(2) Heiminen 2015 Javdraheh 2020	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 1 20.24 (P 2.13 1.23 2 29	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2 6.8 0.57 2.09	20 20 20 22 82 = 3 (P 01) 16 14 55 24	Mean -0.1 1 0.5 1.66 P = 0.15 1.5 0.92 0.5 19	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06	Total 14 14 22 64 44% 14 12 56 24	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.4% 4.3%	Mean Difference IV. Random, 95% CI 9:09 [8:14, 11:66] 12:10[10:46, 13:74] 12:00 [10:41, 13:59] 12:00 [10:41, 13:59] 12:00 [10:30, 14:41] 11:66 [10:53, 12:79] 0:63]-4:18, 54:4] 0:33 [-4:07, 4:59] 1:50 [1:28, 17:2] 0:00 [8:83, 11:17]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(2) Yilmza 2017 Subtotal (95% CI) Heterogeneily: Tau ² = 0.58 Test for overall effect: Z = ; 1.5.2 4-6 weeks Behai: 2015(2) Behai: 2015(2) Heiminen 2015 Javdaneh: 2020 Arm1(1)	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 1 20.24 (P 2.13 1.23 2 2 9 31.09	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2 6.8 0.57 2.09 2.78	20 20 20 22 82 = 3 (P 01) 16 14 55 24 20	Mean -0.1 1 0.5 1.66 P = 0.15 0.92 0.5 19 24.34	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58	Total 14 14 14 22 64 44% 14 12 56 24 20	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.4% 4.3%	Mean Difference IV. Random, 38% CI 9:50 [8:14, 11:66] 12:10 [10:46, 13:74] 12:00 [10:41, 13:59] 12:00 [10:47, 14:41] 11:66 [10:53, 12:79] 0:63 [-4:18, 5:44] 0:31 [-4:07, 6:64] 15:00 [12:8, 4:72] 15:00 [12:8, 4:72] 15:00 [12:8, 4:72]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(3) Yimra 2017 Subtold (95% C1) Heterogeneity: Tau* = 0.58 Test for overall effect: Z = : 1.6.2 4-5 weeks Bahat 2015(1) Bahat 2015(2) Heimiena 2015 Javdrahet 2020-Arm1(1) Nambi 2020-Arm1(1)	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 5 20.24 (P 2.13 1.23 2 29 31.09 37.4	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2 6.8 0.57 2.09 2.78 3.18	20 20 20 20 22 82 = 3 (F 01) 16 14 55 24 20 20 20	Mean -0.1 1 0.5 1.66 P = 0.15 0.92 0.5 19 24.34 30.67	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.88	Total 14 14 14 22 64 44% 14 12 56 24 20 20	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.4% 4.3% 4.2%	Mean Difference IV. Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.45, 13.54] 0.63 [-4.18, 54.4] 0.31 [-4.07, 469] 1.50 [1.28, 1.72] 0.00 [8.83, 11.17] 0.75 [16.08, 8.41] 7.5 [4.68, 8.61]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(3) Yilmza 2017 Subtotal (95% CI) Heterogeneity: Tau ² = 0.58 Test for overall effect: Z = ; 1.5.2 4-6 weeks Behait 2015(2) Behait 2015(2) Heliminen 2015 Javdaneh 2020 Arm1(1) Nambi 2020-Arm1(1) Nambi 2020-Arm1(2) Nambi 2020-Arm1(2) N	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 20.24 (P 2.13 1.23 2 29 31.09 37.4 31.09	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = (0.0000 4.2 6.8 0.57 2.09 2.78 3.18 2.78	20 20 20 22 82 82 83 (P 01) 16 14 55 24 20 20 20	Mean -0.1 1 0.5 1.66 9 = 0.15 1.5 0.92 0.5 19 24.34 30.67 11.72	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.88 2.53	Total 14 14 14 22 64 44% 14 12 56 24 20 20 20	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.4% 4.3% 4.3% 4.2% 4.3%	Mean Difference IV. Random, 38% CI 9:50 [8:14, 11:66] 12:10 [10:46, 13:74] 12:00 [10:41, 13:59] 12:00 [10:47, 14:41] 11:66 [10:53, 12:79] 0:03 [-4:18, 5:44] 0:33 [-4:07, 469] 1:50 [1:28, 4:72] 1:50 [1:28, 4:72] 1:50 [1:28, 4:72] 1:50 [2:08, 4:11] 6:73 [4:63, 6:11] 6:73 [4:63, 6:11] 6:73 [4:63, 6:11] 6:73 [4:63, 6:11] 6:73 [4:63, 6:11]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(3) Viimza 2017 Subtotal (95% C1) Heterogeneity: Tau ² = 0.55 zest for overall effect Z = : 1.6.2 4-5 weeks Behat 2015(1) Behat 2015(2) Heinrien 2015 Javdaneh 2020-Arm1(1) Nambi 2020-Arm1(2) Nambi 2020-Arm2(2) Nambi 2020-Arm2(2)	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 1 20.24 (P 2.13 1.23 2 29 31.09 37.4 31.09 37.4 31.09 37.4	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df= < 0.0000 4.2 6.8 0.57 2.09 2.78 3.18 2.78 3.18	Total 20 20 20 20 22 82 = 3 (P 01) 16 14 55 24 20	Mean -0.1 1 0.5 1.66 9 = 0.15 0.92 0.5 19 24.34 30.67 11.72 19.29	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.88 2.53 2.63	Total 14 14 14 22 64 44% 14 12 56 24 20 20 20 20	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.4% 4.3% 4.3% 4.3% 4.2% 4.2%	Mean Difference IV. Random, 95% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69] 1.50 [12.8, 1.72] 0.00 [8.83, 11.17] 0.75 [15.09, 8.41] 19.37 [17.72, 21.02] 19.37 [17.72, 21.02] 19.37 [17.72, 21.02]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(3) Yilmza 2017 Subtotal (95% C1) Heterogeneity: Tau ² = 0.58 Test for overall effect 2 = ; 1.5.2 4-6 weeks Bahat 2015(2) Bahat 2015(2) Helminien 2015 Javdaneh 2020 Amnil 2020-Amn1(1) Nambi 2020-Am	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 1 20.24 (P 2.13 1.23 2 29 31.09 37.4 31.09 37.4 8.8	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2 6.8 0.57 2.09 2.78 3.18 3.78 3.18 3.42	Total 20 20 20 20 20 22 82 = 3 (P 01) 16 14 55 24 20	Mean -0.1 1 0.5 1.66 9 = 0.15 1.5 0.92 0.5 19 24.34 30.67 11.72 19.29 3.47	3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.88 2.88 2.83 2.63 3.1	Total 14 14 14 22 64 44% 14 12 56 24 20 20 20 20 20 19	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.4% 4.3% 4.3% 4.3% 4.3% 4.2%	Mean Difference IV. Random, 38% CI 9:50 [8:14, 11:66] 12:10 [10:46, 13:74] 12:00 [10:41, 13:59] 12:00 [10:41, 13:59] 12:00 [10:41, 13:59] 12:00 [10:40, 74:41] 11:66 [10:53, 12:79] 15:01 [28, 1:72] 10:00 [8:83, 11:71] 0:75 [5:00; 8:41] 6:73 [4:65, 6:11] 9:37 [17:72, 21:02] 18:11 [16:30, 19:32] 5:33 [2:28, 7:38]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(3) Viimza 2017 Subtotal (95% C1) Heteroganeily: Tau ² e 0.55 Tast for overall effect Z = : Tast for overall effect Z = : Bahat 2015(1) Bahat 2015(2) Heinrianen 2015 Javdaneh 2020-Arm1(1) Nambi 2020-Arm1(2) Nambi 2020-Arm1(2) Saracoglu 2020-Arm1(2) Saracoglu 2020-Arm1(2)	Mean 9.8 13.1 12.5 14.26 8; Chi ² = ± 20.24 (P 2.13 1.23 2 29 31.09 37.4 31.09 37.4 8.8 9.16	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2 6.8 0.57 2.09 2.78 3.18 2.78 3.18 3.42 2.6	20 20 20 20 22 82 = 3 (F 01) 16 14 555 24 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20	-0.1 1 0.5 1.66 2 = 0.15 0.92 0.5 19 24.34 30.67 11.72 19.29 3.47 2.89	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.88 2.63 3.01 3.01	Total 14 14 14 22 64 44% 14 12 56 24 20 20 20 20 20 20 19 19	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.7% 4.4% 4.3% 4.3% 4.3% 4.2% 4.3% 4.2% 4.3%	Mean Difference IV. Random, 92% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69] 1.50 [12.8, 1.72] 0.00 [2.88, 11.17] 6.75 [4.56, 8.61] 19.37 [17.72, 2.10.2] 19.37 [17.72, 2.10.2] 5.33 [12.8, 7.38] 6.27 [4.50, 8.04]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(3) Yilruz 2017 Subiotal (95% C1) Heterogeneity: Tau* = 0.58 Test for overall effect: 2 = : 1.5.2 4-6 weeks Bahat 2015(2) Bahat 2015(2) Heiminen 2015 Javdaneh 2020 Amnib 2020-Amrt1(2) Nambi 2020-Amrt1(1) Nambi 2020-Amrt1(2) Nambi 2020-Amrt1(2) Saracoglu 2020-Amrt(1) Saracoglu 2020-Amrt(1)	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 1 20.24 (P 2.13 1.23 2.2 29 31.09 37.4 31.09 37.4 8.8 9.16 8.8	SD T 1.01 1.75 1.2 2.62 5.31, df = < 0.0000	20 20 20 20 20 22 82 = 3 (F 01) 16 14 555 24 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20 20	-0.1 1 0.5 1.66 -2 = 0.15 1.5 0.92 0.5 19 24.34 30.67 11.72 19.29 3.47 2.89 0.61	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.88 2.63 2.68 2.53 3.1 3.01 2.78	Total 14 14 14 22 64 44% 14 12 56 56 24 20 20 20 20 20 20 19 19 19 18	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.4% 4.3% 4.3% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2%	Mean Difference IV. Random, 95% CI 9.00 [814, 1166] 12.01[104, 15.74] 12.00[104, 15.74] 12.00[104, 15.74] 12.00[104, 15.85] 0.63]-4.18, 5.44] 0.31[-4.07, 469] 1.50[12.8, 12.78] 1.50[12.8, 12.78] 1.50[12.8, 12.78] 1.50[2.8, 12.78] 1.5	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(3) Yilmza 2017 Subtotal (05% C1) Heteroganeily: Tau ² e 0.55 Test for overall effort. Z = : 1.6.2 4-5 weeks Behat: 2015(1) Behat: 2015(2) Heinrianen 2015 Javdaneh 2020-Arm1(1) Nambi 2020-Arm1(2) Nambi 2020-Arm2(2) Saracoglu 2020-Arm2(2) Saracoglu 2020-Arm2(2) Saracoglu 2020-Arm2(2)	Mean 9.8 13.1 12.5 14.26 8; Chi ² = ± 20.24 (P 2.13 1.23 2 29 31.09 37.4 31.09 37.4 8.8 9.16	SD T 1.01 1.75 1.2 2.62 5.31, df = <.0.0000 4.2 6.8 0.57 2.09 2.78 3.18 3.42 2.6 3.42 2.6 3.42 2.6	Total 20 20 20 22 82 3 (P 16 14 55 24 20	-0.1 1 0.5 1.66 -2 = 0.15 1.5 0.92 0.5 19 24.34 30.67 11.72 19.29 3.47 2.89 0.61	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.88 2.63 2.68 2.53 3.1 3.01 2.78	Total 14 14 22 64 444% 14 12 56 24 20 20 20 20 20 20 19 19 18 18 18 18 18 18 19 19 19 19 19 19 19 19 19 19	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.2% 4.3% 4.3% 4.3% 4.2% 4.3% 4.2% 4.3% 4.2%	Mean Difference IV. Random, 95% CI 9.00 [814, 1166] 12.01[104, 15.74] 12.00[104, 15.74] 12.00[104, 15.74] 12.00[104, 15.85] 0.63]-4.18, 5.44] 0.31[-4.07, 469] 1.50[12.8, 12.78] 1.50[12.8, 12.78] 1.50[12.8, 12.78] 1.50[2.8, 12.78] 1.5	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(2) Vilniza 2017 Subiotal (95% C1) Heterogeneity: Tau* = 0.65 Bahat 2015(2) Bahat 2015(2) Heiminen 2015 Javdaneh 2020 Ambi 2020-Amrt (1) Nambi 2020-Amrt (1) Nambi 2020-Amrt (1) Nambi 2020-Amrt (1) Nambi 2020-Amrt (1) Saracoglu 2020-Amrt (1)	Mean 9.8 13.1 12.5 14.26 8; Chi ² = 1 20.24 (P 2.13 1.23 29 31.09 37.4 8.8 9.16	SD T 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2 6.8 0.57 2.09 2.78 3.18 2.78 3.18 3.42 2.6 3.42 2.6 3.42 2.6	Total 20 20 20 22 82 83 (P 16 14 55 24 20	-0.1 1 0.5 1.66 ⁹ = 0.15 1.5 0.92 0.5 19 24.34 30.67 11.72 19.29 3.47 2.89 0.61 0.67	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.68 2.53 2.63 3.01 2.78 3.02	Total 14 14 14 22 64 444% 14 12 56 24 20 20 20 20 20 20 19 19 18 18 28 26 20 20 20 20 20 20 20 20 20 20	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.2% 4.3% 4.3% 4.3% 4.3% 4.2% 4.2% 4.2% 4.2% 4.2% 50.1%	Mean Difference IV. Random, 92% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69] 1.50 [12.8, 1.72] 0.00 [2.88, 11.17] 6.75 [4.56, 8.61] 19.37 [17.72, 2.10.2] 19.37 [17.72, 2.10.2] 5.33 [12.8, 7.38] 6.27 [4.50, 8.04]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(3) Yilmza 2017 Subtotal (05% C1) Heteroganeily: Tau ² e 0.55 Test for overall effort. Z = : 1.6.2 4-5 weeks Behat: 2015(1) Behat: 2015(2) Heinrianen 2015 Javdaneh 2020-Arm1(1) Nambi 2020-Arm1(2) Nambi 2020-Arm2(2) Saracoglu 2020-Arm2(2) Saracoglu 2020-Arm2(2) Saracoglu 2020-Arm2(2)	Mean 9.8 13.1 12.5 14.26 8; Chi² = 1 20.24 (P 2.13 1.23 2 31.09 37.4 31.09 37.4 8.8 9.16 8.8 9.16 64; Chi² =	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2 6.8 0.57 2.09 2.78 3.18 3.42 2.6 3.42 2.6 3.42 2.6 3.42 2.6	Total 20 20 20 20 20 20 20 20 22 82 83 16 14 55 24 20	-0.1 1 0.5 1.66 ⁹ = 0.15 1.5 0.92 0.5 19 24.34 30.67 11.72 19.29 3.47 2.89 0.61 0.67	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.68 2.53 2.63 3.01 2.78 3.02	Total 14 14 14 22 64 444% 14 12 56 24 20 20 20 20 20 20 19 19 18 18 28 26 20 20 20 20 20 20 20 20 20 20	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.2% 4.3% 4.3% 4.3% 4.3% 4.2% 4.2% 4.2% 4.2% 4.2% 50.1%	Mean Difference IV. Random, 95% CI 9.00 [814, 1166] 12.01[104, 15.74] 12.00[104, 15.74] 12.00[104, 15.74] 12.00[104, 15.85] 0.63]-4.18, 5.44] 0.31[-4.07, 469] 1.50[12.8, 12.78] 1.50[12.8, 12.78] 1.50[12.8, 12.78] 1.50[2.8, 12.78] 1.5	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(3) Yimza 2017 Subtotal (65% C1) Heterogeneily: Tau ² = 0.56 Bahat 2015(1) Bahat 2015(2) Heimiana 2015 Javdaneh 2020 Nambi 2020-Arm1(1) Nambi 2020-Arm2(2) Saracoglu 2020-Arm1(2) Nambi 2020-Arm2(2) Saracoglu 2020-Arm2(2) Sar	Mean 9.8 13.1 12.5 14.26 8; Chi² = 1 20.24 (P 2.13 1.23 2 31.09 37.4 31.09 37.4 8.8 9.16 8.8 9.16 64; Chi² =	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df = < 0.0000 4.2 6.8 0.57 2.09 2.78 3.18 3.42 2.6 3.42 2.6 3.42 2.6 3.42 2.6	Total 20 20 20 20 20 20 20 20 22 82 83 16 14 55 24 20	-0.1 1 0.5 1.66 ⁹ = 0.15 1.5 0.92 0.5 19 24.34 30.67 11.72 19.29 3.47 2.89 0.61 0.67	SD 3.26 2.77 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.06 2.58 2.68 2.53 2.63 3.01 2.78 3.02	Total 14 14 14 22 64 444% 14 12 56 24 20 20 20 20 20 20 19 19 18 18 28 26 20 20 20 20 20 20 20 20 20 20	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.2% 4.3% 4.3% 4.3% 4.3% 4.2% 4.2% 4.2% 4.2% 4.2% 50.1%	Mean Difference IV. Random, 95% CI 9.00 [814, 1166] 12.01[104, 15.74] 12.00[104, 15.74] 12.00[104, 15.74] 12.00[104, 15.85] 0.63]-4.18, 5.44] 0.31[-4.07, 469] 1.50[12.8, 12.78] 1.50[12.8, 12.78] 1.50[12.8, 12.78] 1.50[2.8, 12.78] 1.5	
1.6.1 0.3 weeks Majer 2006(2) Majer 2006(2) Majer 2006(3) Yilmza 2017 Subtotal (95% C) Heterogeneity: Tau* = 0.65 East for overall effect. Z = : 1.8.2 + 45 weeks Bahat 2015(2) Bahat 2015(2)	Mean 9.8 13.1 12.25 14.26 8; Chi² = 1 20.24 (P 2.13 1.23 2 29 31.09 37.4 31.09 37.4 8.8 9.16 8.8 9.16 64; Chi² = 3.91 (P <	SD T 1.01 1.75 1.2 2.62 5.31, df = 5.31, df = 6.8 0.57 2.78 3.18 2.78 3.18 3.42 2.6 1065.22 2.6 1065.22 0.0001)	Total 20 20 20 22 82 = 3 (F 01) 16 14 555 24 20 20 20	-0.1 1 0.5 1.66 2 = 0.15 0.92 0.5 19 24.34 30.67 11.72 19.29 0.61 0.67 = 11 (P	SD 3.26 2.77 2.86 3.45 5); I² = 8.3 4.5 0.63 2.86 2.83 2.63 3.01 2.78 3.02 < 0.000	Total 14 14 14 14 22 64 44% 14 12 56 24 20 20 20 20 20 20 20 20 20 20	Weight 4.3% 4.3% 4.2% 17.0% 3.7% 3.8% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.2% 4.3% 4.2% 50.1% 50.1%	Mean Difference IV, Random, 93% CI 9:00 [8:14, 11:66] 12:10 [10:46, 13:74] 12:00 [10:41, 13:59] 12:00 [10:41, 13:59] 12:00 [10:41, 13:59] 12:00 [10:43, 12:79] 0:03 [-4:16, 54:41] 10:00 [8:83 11:17] 6:73 [4:65, 8:61] 19:37 [17:72, 21:02] 18:17 [16:30, 13:92] 19:37 [16:30, 13:62] 19:37 [17:72, 21:02] 18:17 [16:30, 13:92] 19:37 [17:72, 21:02] 18:17 [16:30, 13:92] 19:37 [17:72, 21:02] 18:17 [16:30, 13:92] 19:37 [17:72, 21:02] 19:37 [17:72, 21:02] 19:37 [17:75 [3:86, 11:63]	
1.6.1 0.3 weeks Meijer 2006(2) Meijer 2006(2) Meijer 2006(3) Yilmza 2017 Subtotal (65% C1) Heterogeneily: Tau ² e 0.55 Test for overall effect Z = : 1.6.2 4-5 weeks Behai: 2015(1) Behai: 2015(2) Heinrianen 2015 Javdaneh 2020 Nambi 2020-Arm1(1) Nambi 2020-Arm2(2) Saracoglu 2020 Arm1(2) Saracoglu 2020	Mean 9.8 13.1 12.5 14.26 8; Chi² = 1 14.26 8; Chi² = 2 20.24 (P 2.13 31.09 37.4 9.16 64; Chi² = 4 9.16 64; Chi² = 4 7.3 3.91 (P 7.3	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df af 4.2 6.8 0.57 2.09 4.2 6.8 0.57 2.09 4.2 6.8 3.18 3.42 2.6 1.065 22 6.0001 4.36	Total 20 20 20 20 22 82 = 3 (F 16 14 55 20 1	Mean -0.1 1 0.5 1.66 P = 0.15 0.92	SD 3.26 2.77 2.86 3.45 3.45 0.63 2.06 2.58 2.58 2.58 2.58 2.58 2.58 3.01 2.78 3.02 < 0.000	Total 14 14 14 14 22 64 44% 14 12 56 64 44% 20 20 20 20 20 20 20 20 20 20	Weight 4.3% 4.3% 4.3% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.2%	Mean Difference IV. Random, 95% CI 9,90 [8,14, 11.86] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.78, 14.41] 11.86 [10.33, 12.79] 0.63] [-4.16, 5.44] 0.31 [-4.07, 4.69] 1.50 [1.28, 1.717] 0.75 [5.09, 4.41] 19.37 [17.7, 2.102] 5.33 [12.87, 33] 6.27 [4.50, 8.04] 8.49 [5.69, 10.29] 7.75 [3.86, 11.63] 0.680 [4.59, 9.01]	
1.6.1 0.3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(3) Yilruz 2017 Subtotal (95% C1) Heterogeneity: Tau* = 0.56 Test for overall effect: Z = : 1.8.2 + 5 weeks Bahat 2015(2) Heinrinen 2015(2) Heinrinen 2015 Jandanat 2020 Arm1(2) Nambi 2020-Arm1(2) Nambi 2020-Arm1(2) Nambi 2020-Arm1(1) Nambi 2020-Arm1(2) Nambi 2020-Arm2(1) Nambi 2020-Arm2(1) Nambi 2020-Arm2(1) Nambi 2020-Arm2(1) Saracoglu 2020-Arm2(2) Saracoglu		SD T 1.01 1.75 1.2 2.62 5.31, d1 ≤ 0.0000 4.2 6.8 0.57 2.09 2.78 3.18 3.42 2.6 3.42 2.6 0.0001) 4.36 4.36	Total 20 20 20 22 82 82 82 82 82 16 14 55 24 20 20 37 37	-0.1 1 0.5 1.66 2 = 0.15 0.92 0.5 19 24.34 30.67 11.72 2.89 0.61 0.67 0.6 0.67 0.6 0.6	SD 3.26 2.77 2.86 3.45 5); P = 8.3 4.5 0.63 2.06 2.58 2.63 3.01 2.78 3.02 < 0.000	Total 14 14 14 14 22 64 44% 14 12 566 20 20 20 20 20 20 20 20 20 20	Weight 4.3% 4.3% 4.3% 4.2% 17.0% 3.7% 4.2% 4.2% 4.2% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 50.1% 50.1% 50.1% 4.2% 50.1% 4.2% 50.1% 4.2% 50.1	Mean Difference IV. Random, 98% CI 9.90 [8.14, 11.66] 12.10 [10.46, 13.74] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.41, 13.59] 12.00 [10.31, 13.59] 12.00 [12.81, 72] 15.01 [12.81, 72] 15.01 [12.81, 72] 16.11 [15.03, 19.22] 18.11 [15.03, 19.22] 19.33 [12.01, 62] 2.53 [12.0, 73] 3.53 [12.0, 73	
1.6.1 0.3 weeks Meijer 2006(2) Meijer 2006(2) Meijer 2006(3) Yilmza 2017 Subtotal (65% C1) Heterogeneily: Tau ² e 0.55 Test for overall effect Z = : 1.6.2 4-5 weeks Behai: 2015(1) Behai: 2015(2) Heinrianen 2015 Javdaneh 2020 Nambi 2020-Arm1(1) Nambi 2020-Arm2(2) Saracoglu 2020 Arm1(2) Saracoglu 2020	Mean 9.8 13.1 12.5 14.26 8; Chi² = i 20.24 (P 2.13 1.23 2 31.09 37.4 8.8 9.16 6.4; Chi² = 1 6.4; Chi² = 1 7.3 6.6 5.4	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df af 4.2 6.8 0.57 2.09 4.2 6.8 0.57 2.09 4.2 6.8 3.18 3.42 2.6 1.065 22 6.0001 4.36	Total 20 20 20 20 22 82 = 3 (F 16 14 55 20 1	Mean -0.1 1 0.5 1.66 P = 0.15 0.92	SD 3.26 2.77 2.86 3.45 5); P = 8.3 4.5 0.63 2.06 2.58 2.63 3.01 2.78 3.02 < 0.000	Total 14 14 14 14 22 64 44% 14 12 56 64 44% 20 20 20 20 20 20 20 20 20 20	Weight 4.3% 4.3% 4.3% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.3% 4.2%	Mean Difference IV. Random, 95% CI 9:00 [8:14, 11:86] 12:10 [10:46, 13.74] 12:00 [10:47, 13.59] 12:00 [10:47, 13.59] 12:00 [10:37, 14.41] 11:86 [10:33, 12.79] 0:63] [-4:16, 5.44] 0:31 [-4:07, 459] 1:50 [1:28, 1.72] 1:50 [1:28, 1.7	
1.6.1 0.3 weeks Meijer 2006(2) Meijer 2006(2) Meijer 2006(3) Yilmza 2017 Subtotal (6% C1) Heteroganeily: Tau ² e 0.55 1.6.2 4-5 weeks Behai: 2015(1) Behai: 2015(2) Heinriann 2015 Javdaneh 2020 Nambi 2020-Arm1(1) Nambi 2020-Arm2(2) Saracoglu 2020 Arm1(2) Saracoglu 2020 Arm1(2) Saracoglu 2020 Arm2(2) Saracoglu 2020 Arm2(2)	Mean 9.8 13.1 12.5 14.26 20.24 (P 2.13 1.23 2 29 37.4 31.09 37.4 8.8 9.16 64: Chi ² = 1 7.3 6.6 5.4 14	<u>SD T</u> 1.01 1.75 1.2 2.62 5.31, df -1 2.62 5.31, df -2 2.62 5.31, df -2 2.62 5.31, df -2 2.62 5.31, df -2 2.62 2.78 3.18 3.42 2.6 2.62 5.31, 16 4.2 2.62 5.31, 16 4.2 5.31, 16 5.31, 16 5.34, 12 5.31, 16 5.34, 12 5.31, 16 5.34, 12 5.31, 16 5.34, 12 5.34,	Total 20 20 20 22 82 82 82 82 93 (F 14 555 24 20 20 20 20 20 20 22 82 82 93 (F 9) 93 73 73 73 73 73 73 7	-0.1 1 0.5 1.66 -0.15 1.66 0.92 0.5 19 24.34 11.72 19.29 3.47 2.89 0.61 0.67 0.5 0.66 2.66 7	SD 3.266 2.777 2.866 3.45 5); I ² = 8.3 4.5 0.633 2.58 2.68 2.58 2.68 2.58 2.63 3.01 2.78 3.02 < 0.000	Total 14 14 14 14 22 64 44% 14 12 56 24 20 20 20 20 20 20 20 20 20 20	Weight 4.3% 4.3% 4.3% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2%	Mean Difference IV. Random, 92% CI 9,90 [8,14, 11,86] 12,10 [10,46, 13,74] 12,00 [10,41, 13,59] 12,00 [10,41, 13,59] 12,00 [10,41, 13,59] 12,00 [10,41, 13,59] 12,00 [10,41, 13,59] 12,00 [12,81,72] 0,00 [12,81,717] 0,75 [10,91,441] 19,71 [14,55,861] 19,77 [17,72, 10,92] 5,31 [12,87,30] 19,77 [17,72,10,192] 5,31 [12,87,30] 19,77 [1,72,51,01,92] 5,31 [12,87,30] 6,27 [4,50, 8,04] 8,49 [5,69, 10,29] 7,75 [3,86, 11,63] 6,80 [4,59, 9,01] 6,80 [4,59, 9,01] 6,80 [4,59, 9,01] 1,50 [1,0,64, 3,56] 1,50 [1,0,64, 3,56] 1,50 [1,0,64, 3,56]	
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1.6.1 0-3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(2) Vitruz 2017 Subtotal (95% C) Heterogeneity: Tau* 0.26 Test for overall effect: Z = : 1.8.2 + 5 weeks Bahat 2015(2) Heiminen 2015 Heiminen 2015 Saracoglu 2020-Arm1(2) Saracoglu 2020-Arm2(1) Saracoglu 2020-Arm2(2) Saracoglu 2020-	Mean 9.8 8 13.1 13.1 12.5 14.26 2.13 1.23 2 2.2.24 (P 2.23 2.29 31.09 37.4 33.9.16 8.6 6.6 5.4 6.6 5.4 6.4 Ch ² = 1 3.391 (P <	SD T 1.01 1.75 1.2 2.62 5.31, df - <	Total 20 20 20 20 20 20 20 20 22 82 90 16 14 555 20 37 37	-0.1 1 1 0.5 1.66 0.92 0.5 1.55 0.92 0.5 1.55 0.92 0.61 0.67 0.5 0.66 2.65 0.95 0.67 0.5 0.67 0.67 0.5 0.66 0.5 0.5 0.66 0.95 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.67 0.67 0.5 0.66 0.5 0.5 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	SD 3.266 2.777 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.063 2.63 3.01 2.78 3.02 < 0.000	Total 14 14 14 14 22 64 44% 14 12 56 62 20 20 20 20 20 20 20 20 20 2	Weight 4.3% 4.3% 4.3% 4.2% 17.0% 3.7% 4.2% 4.2% 4.3% 4.2% 4.3% 4.2% 4.3% 4.2% 4.3	Mean Difference IV. Random, 95% CI 9.00 [81, 1166] 12.01[104, 13.24] 12.00[104, 13.24] 12.00[104, 13.24] 12.00[104, 13.26] 0.63]-4.18, 5.44] 0.31[-4.07, 469] 1.50[128, 12.16] 1.50[128, 12.16] 1.50[12	
1.6.1 G-3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(3) Yilmza 2017 Subtotal (65% C) Heterogeneily: Tau ² = 0.55 Test for overall effect Z = : 1.6.2 4-5 weeks Bahat 2015(1) Bahat 2015(2) Heimianen 2015 Javdaneh 2020 Nambi 2020-Arm1(1) Nambi 2020-Arm2(2) Nambi 2020-Arm2(2) Nambi 2020-Arm2(2) Nambi 2020-Arm2(2) Saracoglu 2020-Arm2(2) Subtotal (65% C) Heterogeneily: Tau ² = 4.35 Test for overall effect Z = : 1.6.3 4-9 weeks Ris 2016 Tompson 2016 Subtotal (65% C) Heterogeneily: Tau ² = 4.35 Heterogeneily: T	Mean 9.8 13.1 12.5 14.26 21.33 22.0.24 (P) 2.13 1.23 2.33 2.9 31.09 37.4 8.8 9.16 64: Ch ^P = 7.3 66: Ch ^P = 7.3 66: Ch ^P = 7.3 66: Ch ^P = 1.23 2.16 (P = 1.23 4.7 7.8 68: Ch ^P = 1.23 2.16 (P =	SD T T 1.01 1.75 1.2 2.62 5.31, df 4 4.2 4.2 6.8 0.57 2.09 2.09 2.78 3.18 3.42 2.6 1065 22 1065 22 0.0001) 4.36 4.46 4.46 3.47 5.46.4, 4 0.03) 3.95 9.23 2.96, df 1 1.000000000000000000000000000000000000	Total 20 20 20 20 20 20 20 20 22 82 90 16 14 555 20 37 37	-0.1 1 1 0.5 1.66 0.92 0.5 1.55 0.92 0.5 1.55 0.92 0.61 0.67 0.5 0.66 2.65 0.95 0.67 0.5 0.67 0.67 0.5 0.66 0.5 0.5 0.66 0.95 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.67 0.67 0.5 0.66 0.5 0.5 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	SD 3.266 2.777 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.063 2.63 3.01 2.78 3.02 < 0.000	Total 14 14 14 14 22 64 44% 14 12 56 62 20 20 20 20 20 20 20 20 20 2	Weight 4.3% 4.3% 4.3% 4.2% 17.0% 3.7% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 17.0% 4.3% 50.1% 4.2% 4.3% 50.1% 4.3% 4.3% 50.1% 4.3% 50.1% 5	Mean Difference IV. Random, 92% CI 9,90 [8,14, 11,86] 12,10 [1046, 13,74] 12,00 [104, 13,14] 12,00 [104, 13,14] 12,00 [104, 13,16] 12,00 [104, 13,16] 12,00 [10,16] 0,031 [-4,07, 469] 1,50 [1,28, 1,72] 0,00 [8,83, 11,17] 6,73 [45,6,81] 19,37 [17,72, 21,0] 9,37 [45,6,81] 19,37 [17,72, 21,0] 9,37 [45,6,81] 19,37 [17,72, 21,0] 6,80 [4,59, 9,01] 6,00 [3,78, 2,21] 2,80 [1,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,66, 3,86] -2,50 [-4,43, -0,57] 3,46 [0,32, 6,69] 1,02 [-0,07, 2,11] 4,50 [0,11, 9,69] 1,02 [-0,07, 2,11] 4,50 [0,11, 9,69] 1,02 [-0,07, 2,11] 4,50 [0,11, 9,69] 1,02 [-0,07, 2,11] 1,00 [-0	
1.6.1 0.3 weeks Meijer 2006(2) Meijer 2006(2) Meijer 2006(3) Yilmza 2017 Subbata (16% C) Heterogeneily: Tau ² = 0.55 Test for overall effect Z = : 1.6.2 4-6 weeks Bahat 2015(1) Bahat 2015(2) Heiminen 2015 Javdaneh 2020 Nambi 2020-Arm1(1) Nambi 2020-Arm2(2) Saracoglu 2020-Arm2(2) Subbata (16% C) Heterogeneity: Tau ² = 4.35 Test for overall effect Z = : 1.6.3 7-9 weeks Ris 2016 Tompson 2016 Subbata (16% C) Heterogeneity: Tau ² = 4.35	Mean 9.8 13.1 12.5 14.26 21.33 22.0.24 (P) 2.13 1.23 2.33 2.9 31.09 37.4 8.8 9.16 64: Ch ^P = 7.3 66: Ch ^P = 7.3 66: Ch ^P = 7.3 66: Ch ^P = 1.23 2.16 (P = 1.23 4.7 7.8 68: Ch ^P = 1.23 2.16 (P =	SD T T 1.01 1.75 1.2 2.62 5.31, df 4 4.2 4.2 6.8 0.57 2.09 2.09 2.78 3.18 3.42 2.6 1065 22 1065 22 0.0001) 4.36 4.46 4.46 3.47 5.46.4, 4 0.03) 3.95 9.23 2.96, df 1 1.000000000000000000000000000000000000	Total 20 20 20 20 20 20 20 20 22 82 90 16 14 555 20 37 37	-0.1 1 1 0.5 1.66 0.92 0.5 1.55 0.92 0.5 1.55 0.92 0.61 0.67 0.5 0.66 2.65 0.92 0.5 0.67 0.67 0.5 0.67 0.67 0.5 0.66 0.67 0.5 0.5 0.5 0.5 0.67 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.5 0.67 0.5 0.5 0.5 0.5 0.5 0.66 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	SD 3.266 2.777 2.86 3.45 5); I ² = 8.3 4.5 0.63 2.063 2.63 3.01 2.78 3.02 < 0.000	Total 14 14 14 14 22 64 44% 14 12 56 62 20 20 20 20 20 20 20 20 20 2	Weight 4.3% 4.3% 4.3% 4.2% 17.0% 3.7% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 4.2% 17.0% 4.3% 50.1% 4.2% 4.3% 50.1% 4.3% 4.3% 50.1% 4.3% 50.1% 5	Mean Difference IV. Random, 92% CI 9,90 [8,14, 11,86] 12,10 [1046, 13,74] 12,00 [104, 13,14] 12,00 [104, 13,14] 12,00 [104, 13,16] 12,00 [104, 13,16] 12,00 [10,16] 0,031 [-4,07, 469] 1,50 [1,28, 1,72] 0,00 [8,83, 11,17] 6,73 [45,6,81] 19,37 [17,72, 21,0] 9,37 [45,6,81] 19,37 [17,72, 21,0] 9,37 [45,6,81] 19,37 [17,72, 21,0] 6,80 [4,59, 9,01] 6,00 [3,78, 2,21] 2,80 [1,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,66, 3,86] -2,50 [-4,43, -0,57] 3,46 [0,32, 6,69] 1,02 [-0,07, 2,11] 4,50 [0,11, 9,69] 1,02 [-0,07, 2,11] 4,50 [0,11, 9,69] 1,02 [-0,07, 2,11] 4,50 [0,11, 9,69] 1,02 [-0,07, 2,11] 1,00 [-0	
1.6.1 0-3 weeks Mojer 2006(2) Mojer 2006(2) Mojer 2006(2) Vitruz 2017 Subtotal (65% C) Heterogeneity: Tau* 0.52 East for overall effect: Z = : 1.8.2 + 5 weeks Bahat 2015(2) Heimiann 2015 Heimiann 2015 Heimiann 2015(2) Heimiann 2015(2) Heimiann 2015(2) Heimiann 2015(2) Heimiann 2015(2) Heimiann 2015(2) Heimiann 2015(2) Heimiann 2015(2) Heimiann 2015(2) Saracoglu 2020-Arm1(2) Saracoglu 2020-Arm2(1) Saracoglu 2020-Arm2(2) Saracoglu 2020-Arm2(2) Saracoglu 2020-Arm2(1) Saracoglu 2020-Arm2(2) Saracoglu 2020-Arm2(1) Saracoglu 2020-Arm2(2) Saracoglu 2020-	Mean 9.8 13.1 12.5 14.26 8; Chi² = 20.24 (P 2.13 1.23 2 9.8 9.16 9.16 64: Chi² = 7.3 9.16 64: Chi² = 1.23 6.8 5.4 6.4: Chi² = 1.23 4.7 3.6 5.4 6.8 5.4 6.7 5.4 6.4: Chi² = 1.23 4.7 5.2 6.6 5.4 6.7 6.8 5.4 6.7 6.7 6.8 7.3 6.7 6.7 6.7 6.7 7.3 7.3 7.3 <tr td=""></tr>	SD T 1.01 1.75 1.2 2.262 5.31, df 4 6.8 0.57 2.78 3.18 2.78 3.18 3.18 3.42 2.6 1.0055 22 0.0001 4.36 4.36 4.36 4.36 4.36 3.47 54.64, 6 0.03) 3.95 2.39, df 1 0.21)	Total 20 20 20 20 20 20 22 82 87 16 14 555 24 20 20 21 131 145 101 29 130 131 11 20	Mean -0.1 1 0.5 1.66 2 = 0.15 0.92 0.5 19 24.34 0.67 11.72 19.29 0.61 0.67 11.72 19.29 0.61 0.67 7 -2.5 -0.5 (P < 0 0.67 0.67 0.67 0.67 0.67 0.67 0.67 0.67 0.67 0.72 0.67 19 0.67 0.67 0.67 0.67 0.67 0.72 0.67 0.67 0.72 0.67 0.62 0.67 0.62 0.67 0.62 0.67 0.62 0.67 0.21 -0.22 0.22	SD 3.26 2.77 2.86 3.45 5); I* = 8.3 4.5 0.63 2.68 2.68 2.68 2.68 2.68 2.68 2.68 2.53 2.63 3.01 2.78 3.01 2.78 3.01 2.78 3.01 2.78 3.01 2.78 3.01 2.78 3.01 2.78 3.01 3.03 1.67 0.84 .000011 3.93 9.23 20; I*	Total 14 14 14 14 14 22 64 44% 14 12 56 62 20 20 20 20 20 20 20 20 20 2	Weight 4.3% 4.3% 4.2% 4.3% 4.2% 4.3% 4.2% 4.3% 4.4% 4.3% 4.2% 4.2%	Mean Difference IV. Random, 92% CI 9,90 [8,14, 11,86] 12,10 [1046, 13,74] 12,00 [104, 13,14] 12,00 [104, 13,14] 12,00 [104, 13,16] 12,00 [104, 13,16] 12,00 [10,16] 0,031 [-4,07, 469] 1,50 [1,28, 1,72] 0,00 [8,83, 11,17] 6,73 [45,6,81] 19,37 [17,72, 21,0] 9,37 [45,6,81] 19,37 [17,72, 21,0] 9,37 [45,6,81] 19,37 [17,72, 21,0] 6,80 [4,59, 9,01] 6,00 [3,78, 2,21] 2,80 [1,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,64, 3,86] 1,50 [-2,66, 3,86] -2,50 [-4,43, -0,57] 3,46 [0,32, 6,69] 1,02 [-0,07, 2,11] 4,50 [0,11, 9,69] 1,02 [-0,07, 2,11] 4,50 [0,11, 9,69] 1,02 [-0,07, 2,11] 4,50 [0,11, 9,69] 1,02 [-0,07, 2,11] 1,00 [-0	
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(c)

Figure 4. Cont.

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random. 95% C	IV. Random, 95% CI
1.3.1 0-12 weeks									
Bahat 2015(1)	2.13	4.2	16	1.5	8.3	14	3.7%	0.63 [-4.18, 5.44]	
Bahat 2015(2)	1.23	6.8	14	0.92	4.5	12	3.8%	0.31 [-4.07, 4.69]	
Gardner 2019(1)	7.3	4.36	37	0.5	5.37	38	4.2%	6.80 [4.59, 9.01]	
Gulsen 2020	14	4.65	8	7	4.3	8	3.8%	7.00 [2.61, 11.39]	
Gustavsson 2006(1)	-1	3.47	13	-2.5	1.67	16	4.2%	1.50[-0.56, 3.56]	
Helminen 2015	2	0.57	55	0.5	0.63	56	4.4%	1.50 [1.28, 1.72]	
Javdaneh 2020		2.09	24	19	2.06	24	4.4%	10.00 [8.83, 11.17]	-
Meijer 2006(1)	9.8	1.01	20	-0.1	3.26	14	4.3%	9.90 [8.14, 11.66]	
Nambi 2020-Arm1(1)	31.09	2.78	20	24.34	2.58	20	4.3%	9.90 [0.14, 11.00]	
								6.75 [5.09, 8.41]	
Nambi 2020-Arm2(1)	31.09	2.78	20	11.72	2.53	20	4.3%	19.37 [17.72, 21.02]	
Saracoglu 2020-Arm1(1)		3.42	20	3.47	3.1	19	4.2%	5.33 [3.28, 7.38]	
Saracoglu 2020-Arm1(2)	9.16	2.6	20	2.89	3.01	19	4.3%	6.27 [4.50, 8.04]	
Saracoglu 2020-Arm2(1)		3.42	20	0.61	2.78	18	4.2%	8.19 [6.22, 10.16]	
Saracoglu 2020-Arm2(2)	9.16	2.6	20	0.67	3.02	18	4.2%	8.49 [6.69, 10.29]	
Yilmza 2017	14.26	2.62	22	1.66	3.45	22	4.2%	12.60 [10.79, 14.41]	
Subtotal (95% CI)			329			318	62.3%	7.08 [3.98, 10.17]	•
Heterogeneity: Tau ² = 35.7				14 (P <	0.000	01); 2 :	= 99%		
Test for overall effect: Z = 4	4.48 (P •	< 0.000	01)						
1.3.2 13-24 weeks									
Gardner 2019(2)	6.6	4.38	37	0.6	5.34	38	4.2%	6.00 [3.79, 8.21]	
Gustavsson 2006(2)		3.47	13	-0.5	0.84	16	4.2%	-2.50[-4.43, -0.57]	
Meiler 2006(2)	13.1	1.75	20	-0.0	2.77	14	4.3%	12.10 [10.46, 13.74]	
Nambi 2020-Arm1(2)	37.4		20	30.67	2.88	20	4.3%	6.73 [4.85, 8.61]	
	37.4		20	19.29	2.63	20	4.2%		
Nambi 2020-Arm2(2)			101			20		18.11 [16.30, 19.92]	-
Ris 2016		3.95		0.21	3.93		4.3%	1.02[-0.07, 2.11]	
Tompson 2016	4.7	9.23	29	-0.2	9.23	28	3.7%	4.90 [0.11, 9.69]	
Subtotal (95% CI)			240			235	29.2%	6.64 [1.16, 12.13]	
Heterogeneity: Tau ² = 53.3 Test for overall effect: Z = 3	32; Chi ² = 2.37 (P =	= 380.2 = 0.02)	4, df =	6 (P <	0.0000	1); 2 =	98%		
1.3.3 More than 24 weeks									
Gardner 2019(3)		4.64	37	20	5.34	38	4.2%	2.80 [0.54, 5.06]	
Garoner 2019(3) Meijer 2006(3)	12.5	1.2	20		2.86	14	4.2%	12.00 [10.41, 13.59]	-
Meijer 2006(3)	12.5	1.2	20	0.5	2.86	14	4.3%	12.00 [10.41, 13.59]	
Subtotal (95% CI)	-							7.44 [-1.58, 16.45]	States and a second
Heterogeneity: Tau ² = 41.3 Test for overall effect: Z = 1			, di =	I (P C U	.00001); = = 5	10 %		
Total (95% CI)			626			605	100.0%	6.99 [4.59, 9.38]	•
						005	100.076	0.33 [4.03, 3.30]	
Heterogeneity: Tau ² = 34.2						001); P	= 99%		-20 -10 0 10 20
		- 1040	J4, UI						
	5.72 (P	< 0.000	01)						
	5.72 (P	< 0.000	01)			= 0%			Uni-Modal Multi-Modal
	5.72 (P	< 0.000	01)			= 0%			
	5.72 (P	< 0.000	01)			= 0%			
	5.72 (P	< 0.000	01)			= 0%	(d)	1	
Test for overall effect: Z = t Test for suboroup differenc	5.72 (P + ces: Chi ² Mul	< 0.000 = 0.03	101) 1. df = 3 al	2 (P = 0 Uni	.99), I² -Moda	I	(d)	Mean Difference	Uni-Modal Multi-Modal Mean Difference
Test for suboroup differences	5.72 (P - ces: Chi ² Mul Mean	< 0.000 ' = 0.03 ti-Mod SD	01) . df = : al <u>Total</u>	2 (P = 0 Uni Mean	.99), I² -Moda	I			Uni-Modal Multi-Modal Mean Difference
Test for subaroup differences subaroup differences subaroup study or Subgroup 1.5.1 Psychological thera	5.72 (P + ces: Chi ² Mult <u>Mean</u> apy+ Exe	< 0.000 = 0.03 ti-Mod <u>SD</u> ercise	al Total vs. Ex	Q (P = 0 Un <u>Mean</u> ercise	.99), P I-Moda SD	I Total	(d) Weight	Mean Difference IV. Random. 95% Cl	Uni-Modal Multi-Modal Mean Difference
Test for subgroup differences Study or Subgroup 1.5.1 Psychological thera Bahat 2015(1)	5.72 (P + ces: Chi ² Mult <u>Mean</u> apy+ Exc 2.13	< 0.000 = 0.03 ti-Mod SD ercise 4.2	01) al <u>Total</u> vs. Ex 16	2 (P = 0 Un Mean ercise 1.5	.99). I ² I-Moda SD 8.3	I Total 14	(d) <u>Weight</u> 4.2%	Mean Difference IV. Random. 95% Cl 0.63[-4.18, 5.44]	Uni-Modal Multi-Modal Mean Difference
Test for subgroup differences Study or Subgroup 1.5.1 Psychological thera Bahat 2015(1)	5.72 (P + ces: Chi ² Mult <u>Mean</u> apy+ Exe	< 0.000 = 0.03 ti-Mod <u>SD</u> ercise	al Total vs. Ex	Q (P = 0 Un <u>Mean</u> ercise	99), P I-Moda SD	I Total	(d) Weight	Mean Difference IV. Random. 95% Cl	Uni-Modal Multi-Modal Mean Difference
Test for subbroup differences Study or Subgroup 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2)	5.72 (P + ces: Chi ² Mul <u>Mean</u> apy+ Exe 2.13 1.23	< 0.000 = 0.03 ti-Mod SD ercise 4.2	01) al <u>Total</u> vs. Ex 16	2 (P = 0 Un Mean ercise 1.5	.99). I ² I-Moda SD 8.3	I Total 14	(d) <u>Weight</u> 4.2%	Mean Difference IV. Random. 95% Cl 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69]	Uni-Modal Multi-Modal Mean Difference
Test for subproup differences Study or Subgroup 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2) Gardner 2015(1)	5.72 (P - ces: Chi ^a Mul <u>Mean</u> apy+ Exc 2.13 1.23 7.3	< 0.000 = 0.03 ti-Mod SD ercise 4.2 6.8 4.36	al Total vs. Ex 16 14 37	Uni Mean ercise 1.5 0.92 0.5	99). P I-Moda SD 8.3 4.5 5.37	I Total 14 12	(d) Weight 4.2% 4.4% 4.8%	Mean Difference IV. Random. 95% Cl 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69] 6.80 [4.59, 9.01]	Uni-Modal Multi-Modal Mean Difference
Test for subaroup difference Study or Subgroup 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2) Gardner 2019(2)	5.72 (P ces: Chi ^a Mult <u>Mean</u> apy+ Exc 2.13 1.23 7.3 6.6	< 0.000 = 0.03 ti-Mod SD arcise 4.2 6.8 4.36 4.38	al Total vs. Ex 16 14 37 37	Uni Mean ercise 1.5 0.92 0.5 0.6	99), P I-Moda SD 8.3 4.5 5.37 5.34	I Total 14 12 38 38	(d) Weight 4.2% 4.4% 4.8% 4.8%	Mean Difference IV. Random, 95% Cl 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69] 6.80 [4.59, 9.01] 6.00 [3.79, 8.21]	Uni-Modal Multi-Modal Mean Difference
Test for suboroup difference Study or Subgroup 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2) Garcher 2019(1) Garcher 2019(3)	5.72 (P + ces: Chi ^a Mult <u>Mean</u> apy+ Exe 2.13 1.23 7.3 6.6 5.4	< 0.000 = 0.03 ti-Mod SD ercise 4.2 6.8 4.36 4.38 4.38 4.64	al Total vs. Ex 16 14 37 37 37	Un Mean ercise 1.5 0.92 0.5 0.6 2.6	.99), P I-Moda SD 8.3 4.5 5.37 5.34 5.34	I Total 14 12 38 38 38 38	(d) Weight 4.2% 4.4% 4.8% 4.8% 4.8%	Mean Difference IV. Random. 95% Cl 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69] 8.80 [4.59, 9.01] 6.00 [3.79, 8.21] 2.80 [0.54, 5.06]	Uni-Modal Multi-Modal Mean Difference
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Test for suboroup difference Study or Subgroup 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2) Garcher: 2019(2) Garcher: 2019(2) Garcher: 2019(3) Guiden 2020 Juvdaneh 2020	5.72 (P - ces: Chi ^a Mul Mean 123 7.3 6.6 5.4 14 29	< 0.000 = 0.03 ti-Mod SD ercise 4.2 6.8 4.36 4.36 4.38 4.64 4.65 2.09	al total vs. Ex 16 14 37 37 37 8 24	Uni Mean ercise 1.5 0.92 0.6 2.6 7 19	99). P I-Moda SD 8.3 4.5 5.37 5.34 5.34 4.3 2.06	I Total 14 12 38 38 38 38 38 24	(d) Weight 4.2% 4.4% 4.8% 4.8% 4.8% 4.4% 4.9%	Mean Difference IV. Random. 95% Cl 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69] 6.80 [4.59, 9.01] 5.00 [3.79, 621] 2.80 [0.54, 5.06] 7.00 [2.61, 11.39] 10.00 [8.83, 11.17]	Uni-Modal Multi-Modal Mean Difference
Test for suboroup differences Study or Subgroup 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2) Garriere 2018(2) Garriere 2018(2) Garriere 2018(2) Jandano 2020 Jandano 2020 Jandano 2020	5.72 (P + ces: Chi ^a Mul Mean 1py+ Exe 2.13 1.23 7.3 6.6 5.4 14 29 31.09	< 0.000 = 0.03 ti-Mod SD ercise 4.2 6.8 4.36 4.36 4.38 4.64 4.65 2.09 2.78	al Total vs. Ex 16 14 37 37 8 24 20	Uni Mean ercise 1.5 0.92 0.5 0.6 2.6 7 19 24.34	.99). P I-Moda SD 8.3 4.5 5.37 5.34 5.34 4.3 2.06 2.58	I Total 14 12 38 38 38 38 38 24 20	(d) Weight 4.2% 4.4% 4.8% 4.8% 4.8% 4.8% 4.9% 4.8%	Mean Difference IV. Random. 95% CI 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69] 6.80 [4.59, 9.01] 6.00 [3.79, 8.21] 1.260 [0.84, 5.06] 7.00 [2.61, 11.39] 10.00 [8.83, 11.17] 6.75 [50, 8.41]	Uni-Modal Multi-Modal Mean Difference
Test for suboroup differences Study or Subgroup 1.5.1 Psychological thera Bahat 2015(1) Gardner 2015(2) Gardner 2015(3) Gardner 2015(3) Gardner 2015(3) Gardner 2015(3) Marbil 2020-Arm1(1) Nambil 2020-Arm1(2)	5.72 (P - ces: Chi ² Mult Mean apy+ Exc 2.13 1.23 7.3 6.6 5.4 14 29 31.09 37.4	< 0.000 = 0.03 ti-Mod SD ercise 4.2 6.8 4.36 4.36 4.36 4.36 4.64 4.65 2.09 2.78 3.18	al Total vs. Ex 16 14 37 37 8 24 20 20	Uni Mean ercise 1.5 0.92 0.5 0.6 2.6 7 19 24.34 30.67	.99). P I-Moda SD 8.3 4.5 5.37 5.34 5.34 4.3 2.06 2.58 2.88	I <u>Total</u> 14 12 38 38 38 38 24 20 20	(d) 4.2% 4.4% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8	Mean Difference IV. Random. 95% Cl 0.63 [-4.18, 5.44] 0.31 [-4.07, 4.69] 6.80 [4.59, 9.01] 6.00 [3.79, 8.21] 2.80 [0.54, 5.06] 7.00 [2.61, 11.39] 10.00 [8.83, 11.17] 6.75 [5.09, 8.41] 6.73 [4.58, 8.61]	Uni-Modal Multi-Modal Mean Difference
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Test for suboroup difference Study or Suboroup 1.5.1 Psychological thera Bahat 2016(1) Bahat 2016(1) Bankar 2016(2) Barniner 2018(2) Barniner 2020-Arm1(1) Namil 2020-Arm2(1) Namil 2020-Arm2(1) Saracopiu 2020-Arm2(1) Saracopiu 2020-Arm2(1) Saracopiu 2020-Arm2(1) Castaroson 2006(2) Custarsson 2006(2) Gustarsson 2006(2)	Muti Maan npy+ Exc 2.13 7.3 7.3 7.3 7.3 7.3 7.3 7.3 7.3 7.3 7.	c 0.000 = 0.03 ti-Mod SD ercise 4.2 6.8 4.36 4.36 4.34 4.65 2.76 3.18 2.78 3.18 2.78 3.18 2.76 3.18 2.76 3.18 2.76 3.18 2.76 3.18 2.76 3.18 2.76 3.18 2.76 3.18 2.76 3.18 2.76 3.18 2.76 3.18 2.76 3.18 2.76 3.18 3.42 3.42 3.42 3.47 3.47 3.47	al Total vs. Ex 166 14 37 37 8 24 200 200 200 200 200 200 200	Uni Mean orcise 1.5 0.62 24.34 30.67 19 24.34 11.72 19.29 0.61 0.67 12 (P < Passive - 2.5 - 0.5	99). P -Moda SD 8.3 4.5 5.37 5.34 4.3 2.68 2.63 2.63 2.63 3.02 0.0000 PT 1.67 0.84	I 14 12 38 38 38 24 20 20 20 18 28 28 20 20 10 11 18 18 28 20 20 10 10 11 12 12 12 12 12 12 12 12 12	(d) Waight 4.2% 4.4% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8	Mean Difference IV. Random. 95% Cf 0.63]-4.18, 5.44] 0.31]-4.07, 459] 6.80 (4.59, 9.01] 8.00 (3.79, 241) 1.260 (0.54, 5.06] 7.00 (2.64, 1.137) 6.75 (0.06, 8.41) 1.50 (1.05, 1.66) 1.50 (1.05, 1.	Uni-Modal Multi-Modal Mean Difference
Test for suboroup difference Study or: Subproup 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2) Gardner 2019(2) Gardner 2019(2) Gardner 2019(2) Javalanoh 2020 Javadanoh 2020 Javadanoh 2020 Javadanoh 2020 Arm2(1) Nambi 2020-Arm2(1) Saracoglu 2020-Arm2(1) Saracoglu 2020-Arm2(1) Saracoglu 2020-Arm2(1) Saracoglu 2020-Arm2(1) Guistareson 2006(2) Test for overall effect: Z = 1 1.5.2 Psycholocigal thera Guistareson 2006(2) Guistareson 2006(2) Guistareson 2006(2) Heiminen 215	Mut <u>Maan</u> <u>1</u> <u>2</u> <u>1</u> <u>2</u> <u>1</u> <u>2</u> <u>1</u> <u>2</u> <u>1</u> <u>2</u> <u>1</u> <u>2</u> <u>1</u> <u>2</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>1</u> <u>2</u> <u>1</u> <u>1</u> <u>1</u> <u>1</u> <u>1</u> <u>1</u> <u>1</u> <u>1</u>	c 0.000 = 0.03 ti-Mod SD ercise 4.2 6.8 4.36 4.36 4.36 4.36 2.76 3.16 2.78 3.18 3.27 2.6 c.0000 essive 3.47 3.47 0.57	001) di di = : di Total Total vs. Exx 16 14 37 37 8 24 20 20 20 20 20 20 20 20 20 20	Uni Mean ercise 1.55 0.92 0.5 0.66 2.66 7 19 9.24.34 30.67 7 11.72 9.61 0.61 0.67 12 (P < Passive -2.5 0.5 0.5 0.5	99). P -Moda SD 8.3 4.5 5.34 5.34 4.3 2.66 2.58 2.63 2.63 2.78 3.02 0.0000 PT 1.67 0.84 0.63	I Total 14 12 38 38 8 24 20 20 20 20 20 20 20 20 20 20	(d) Weight 4.2% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 61.2% 96%	Mean Difference IV. Random, 95% Cf 0.63]-4.18, 5.44] 0.31]-4.07, 469] 6.80 [4.59, 9.01] 8.00 [3.79, 8.21] 2.00 [0.54, 5.06] 7.00 [2.61, 11.39] 1.57 [4.65, 8.61] 19.37 [17.72, 2.102] 7.97 [5.03, 410, 19.22] 7.97 [5.03, 40, 10.91] 1.50[-0.56, 3.56] -2.50[-4.43, -0.57] 1.50[-2.8, 17.2]	Uni-Modal Multi-Modal Mean Difference
Test for suboroup differences Study or Suboroup 1.5.1 Psychological thera Bahat 2016(1) Bahat 2016(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Mambi 2020-Am2(2) Saracopiu 2020-Am2(2) Saracopiu 2020-Am2(2) Saracopiu 2020-Am2(2) Saracopiu 2020-Am2(2) Saracopiu 2020-Am2(2) Saracopiu 2020-Am2(2) Gardner 2018(2) Heterogonety: Tau ² = 27 A Test for overall effect Z = 1 Gustavsson 2006(2) Hetminen 2015	5.72 (P - Y Muti Mean npy+Ex: 2.13 1.23 7.3 6.6 5.4 1.23 7.3 6.6 5.4 1.23 7.3 6.6 5.4 1.23 7.3 8.6 8.9 9.16 1.7 Chi ² - Chi ² - C	< 0.000 = 0.03 II-Mod SD SD e 4.2 6.8 4.36 4.36 4.436 4.64 4.65 2.78 3.18 3.18 3.27.2 2.6 SD SD SD	001) diff = 3 al <u>Total</u> 16 17 16 14 37 37 37 37 37 37 37 37 20 20 20 20 20 20 20 20 20 20	Uni Mean ercise 1.55 0.92 24.34 30.67 11.72 19.29 0.61 0.67 12 (P < Passive -2.5 0.5 0.5 0.5	99). P -Moda SD 8.3 4.5 5.34 4.3 2.68 2.58 2.63 2.78 3.02 0.0000 PT 1.67 0.84 0.63 3.26	I Total 14 12 38 38 8 24 20 20 20 20 20 20 20 20 20 20	(d) Weight 4.2% 4.4% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8%	Mean Difference IV. Random. 95% CI 0.63]-4.18, 5.44] 0.31]-4.07, 469] 6.80 (4.59, 9.01] 8.00 (3.79, 2.21) 1.260 (0.54, 5.06) 7.00 (2.63, 11.17) 8.75 [5.03, 8.41] 1.50, 7.65, 5.82 1.150, 7.65, 5.82 1.50, 1.056, 3.869] 1.50, 1.028, 1.727 1.50, 1.28, 1.727 1.50, 1.50, 1.50, 1.507 1.50, 1.50, 1.507 1.50, 1.50, 1.507 1.50, 1.507 1.50, 1.507 1.50, 1.507 1.50, 1.507 1.50, 1.507 1.50, 1.507 1.50	Uni-Modal Multi-Modal Mean Difference
Test for suboroup difference Study or: Suboroup 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2) Gardner 2019(2) Gardner 2019(2) Gardner 2019(2) Javdanch 2020 Javdanch 2020 Javdanch 2020 Javdanch 2020 Stanciglu 2020-Arm1(1) Nambi 2020-Arm2(1) Starcoglu 2020-Arm2(1) Starcoglu 2020-Arm2(1) Vastino 1020-Arm2(1) Starcoglu 2020-Arm2(1) Guistareson 2008(1) Guistareson 2008(1) Guistareson 2008(1) Guistareson 2008(2) Guistareson 2008(2)	Mult Man apy+ Exec 2.13 1.23 7.3 31.09 37.4 37.3 37.3 37.3 37.3 37.3 37.3 37.3	c 0.000 = 0.03 SD ercise 4.2 6.8 4.36 4.36 4.36 4.36 4.36 4.36 4.36 2.09 2.78 3.18 2.78 3.18 2.78 3.18 2.76 3.42 2.6 = 327.2 c.6 3.42 2.6	001) di di = : al Total vs. Ex 16 14 37 37 8 24 20 20 20 20 20 20 20 20 20 20	Uni Mean ercise 1.5 0.6 2.6 7 9 24.34 30.67 19.29 0.61 0.67 12 (P < Passivv - 2.5 0.5 0.5 0.5 10 11	99). P -Moda SD 8.3 4.5 5.37 5.34 5.34 2.58 2.53 2.68 2.53 2.68 2.53 3.02 0.0000 PT 1.67 0.84 0.63 3.26 2.77	I Total 14 12 38 38 8 20 20 20 20 20 20 20 20 20 20	(d) Weight 4 2% 4 4% 4 4% 4 4% 4 4% 4 4% 4 4% 4 4%	Mean Difference IV Random, 95% Cl 0.63] - 4.18, 5.44] 0.63] - 4.07, 469] 640 [57, 9, 27] 2.00 [24, 57, 9, 27] 2.00 [24, 57, 9, 27] 7.00 [24, 11, 39] 10.00 [83, 11, 17] 7.75 [50, 9, 841] 6.73 [425, 861] 1.537 [17, 72, 21, 02] 8.19 [522, 10, 16] 8.49 [669, 10, 29] 7.97 [50, 3, 16, 9] 1.50[-0.56, 3, 86] -2.50[-0.44, 0, 057] 1.50 [1.28, 172] 9.90 [814, 1166] 1.21 [01, 04, 13, 74]	Uni-Modal Multi-Modal Mean Difference
Test for suboroup difference Study or Subgroup 1.5.1 Psychological threa Bahat 2016(1) Bahat 2016(1) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Mambi 2020-Arm1(2) Nambi 2020-Arm1(2) Nambi 2020-Arm2(1) Nambi 2020-Arm2(2) Saracopiu 2020-Arm2(2) Saracopiu 2020-Arm2(2) Gustavesco 2006(2) Gustavesco 2006(2) Heinrignen 2015 Meijer 2006(2)	Mult Mean npp+Exc 2.13 1.23 6.6 5.4 14 29.9 37.4 8.10 9.16 5.51 (P - 9.17 CP ² = 5.51 (P - 9.16 - 1 - 3 2 9.8 13.1 12.5	< 0.000 = 0.03 II-Mod SD II-Mod SD II-CISE 4.2 6.8 4.36 4.36 4.36 4.36 4.36 4.36 4.36 4.36 2.76 3.18 3.42 2.76 3.18 3.42 2.76 3.18 3.42 2.6 5.0000 II-DIF II-DIF 1.01 1.75 1.01 1.75	001) . df = : al Total vs. Ex 16 14 37 37 8 24 20 20 20 20 20 20 20 20 20 20	Uni Mean ercise 1.55 0.92 24.34 30.67 11.72 19.29 0.61 0.67 12 (P < Passive -2.5 0.5 0.5 0.5	99). P -Moda SD 8.3 4.5 5.34 4.3 2.68 2.58 2.63 2.78 3.02 0.0000 PT 1.67 0.84 0.63 3.26	I 14 12 38 38 38 24 20 20 20 20 20 20 20 18 288 288 288 288 21 1); I ² - 16 16 16 16 16 14 14 12 14 12 14 12 14 12 14 12 14 12 14 12 14 12 14 12 14 12 14 12 12 14 12 12 12 12 12 12 12 12 12 12	(d) Waight 4.2% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8	Mean Difference IV. Random. 95% CI 0.63]-4.18, 5.44] 0.63]-4.07, 469 6.80 (4.59, 9.01] 8.00 (13.79, 2-21) 2.26 (D.54, 5.06] 7.00 (2.64, 1.13) 8.75 (4.65, 5.61) 1.57 (4.65, 5.61) 1.57 (4.65, 5.61) 1.57 (5.03, 10.91) 1.50 (-0.56, 3.56] 2.50 (-4.43, -0.57) 1.50 (1.28, 1.72) 9.90 (3.14, 11.66) 1.20 (10.44, 13.74)	Uni-Modal Multi-Modal Mean Difference
Test for suboroup difference Study or, Subprove 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2) Barbat 2015(2) Barbat 2015(2) Garciner 2019(2) Garciner 2019(2) Barbat 2020 Javdanch 2020 Javdanch 2020 Starcoglu 2020-Arm1(1) Nambi 2020-Arm2(1) Nambi 2020-Arm2(1) Starcoglu 2020-Arm2(1) Starcoglu 2020-Arm2(1) Guistavason 2008(1) Guistavason 2008(1) Guistavason 2008(1) Guistavason 2008(2) Heijer 2008(1) Meijer 2008(2) Meijer 2008(2) Meijer 2008(2) Meijer 2008(2)	Mult Man apy+ Exec 2.13 1.23 7.3 31.09 37.4 37.3 37.3 37.3 37.3 37.3 37.3 37.3	< 0.000 = 0.03 II-Mod SD II-Mod SD II-CISE 4.2 6.8 4.36 4.36 4.36 4.36 4.36 4.36 4.36 4.36 2.76 3.18 3.42 2.76 3.18 3.42 2.76 3.18 3.42 2.6 5.0000 II-DIF II-DIF 1.01 1.75 1.01 1.75	001) . df = : al Total vs. Ex 16 14 37 37 37 37 37 20 20 20 20 20 20 20 20 20 20	Uni Mean 1.5 0.92 0.5 0.6 24.34 11.72 19.29 0.67 11.72 19.29 0.67 12 (P < -2.5 0.5 -0.5 0.5 -0.1 1 0.5	99). P -Moda SD 8.3 4.5 5.37 5.34 5.34 2.58 2.53 2.68 2.53 2.68 2.53 3.02 0.0000 PT 1.67 0.84 0.63 3.26 2.77	I Total 14 12 38 38 38 38 24 20 20 20 20 20 18 288 288 201); P 16 166 166 14 14 14 22 20 20 20 20 20 20 20 20 20	(d) Waight 4.2% 4.4% 4.4% 4.4% 4.8%	Mean Difference IV Random. 95% Cf 0.63] - 4.18, 5.44] 0.31] - 4.07, 459 2.800 (54, 50, 61) 2.200 (54, 50, 61) 2.200 (54, 50, 61) 7.00 (26, 11, 139) 10.00 (83, 11, 17) 10.07 (83, 11, 17) 10.77 (5 100, 84, 11) 10.37 (17, 72, 21, 02) 18.11 (163, 0, 1922) 18.19 (522, 10, 16) 8.49 (560, 10, 29) 7.37 (5, 03, 16, 91) 1.50 (-0.56, 3.56) -2.50 (-4.40, -0.57) 1.50 (128, 172) 9.50 (814, 1166) 2.10 (10.44, 13.74) 12.00 (10.74, 14.41) 2.00 (10.74, 14.41)	Uni-Modal Multi-Modal Mean Difference
Test for suboroup difference Study or Subproup 1.5.1 Psychological thera Bahat 2015(1) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Mambi 2020-Arm1(1) Nambi 2020-Arm2(1) Value 2000-Arm2(1) Nambi 2020-Arm2(1) Value 2000-Arm2(1) Nambi 2020-Arm2(1)	Mult Mean App + Exc 2.13 3.2 3.3 6.6 5.4 14 2.19 3.7 4 3.109 3.7 4 8.6 9.16 9.3 7.4 8.8 9.16 9.3 7.4 8.8 9.16 9.3 7.4 9.3 7.4 3.7 9.4 9.3 7.4 3.7 9.4 9.3 7.4 9.3 7.4 3.7 9.3 7.4 3.7 9.3 7.4 3.7 9.3 7.4 3.7 9.3 7.4 3.7 9.4 9.3 7.4 3.7 9.7 9.3 7.4 3.7 9.7 9.3 7.4 9.7 9.3 7.4 9.7 9.3 7.4 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7	< 0.000 = 0.03 ti-Model SD precise 4.2 6.8 4.36 4.36 2.76 3.18 3.18 3.278 3.18 3.18 3.272 c.000 ssive ssive 3.47 0.57 1.01 1.75 1.2 2.62	001) . df = : al Total vs. Ex 16 14 37 37 37 37 37 37 37 37 37 37	Uni Mean 1.5 0.92 0.5 24.34 30.67 19 24.34 30.67 12 (P < Passive -2.5 0.5 -0.5 0.5 1.66	99). P -Moda SD 8.3 4.5 5.34 4.3 2.68 2.58 2.58 2.68 2.58 2.63 2.78 3.02 0.0000 PT 1.67 2.87 3.26 3.	I Total 14 12 38 38 38 38 24 200 200 200 200 200 200 200	(d) Waight 4.2% 4.4% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8	Mean Difference IV. Random. 95% CI 0.63]-4.18, 5.44] 0.63]-4.07, 469 6.80 (4.59, 9.01] 8.00 (13.79, 2-21) 2.26 (D.54, 5.06] 7.00 (2.64, 1.13) 8.75 (4.65, 5.61) 1.57 (4.65, 5.61) 1.57 (4.65, 5.61) 1.57 (5.03, 10.91) 1.50 (-0.56, 3.56] 2.50 (-4.43, -0.57) 1.50 (1.28, 1.72) 9.90 (3.14, 11.66) 1.20 (10.44, 13.74)	Uni-Modal Multi-Modal Mean Difference
Test for suboroup difference Study or Subproup 1.5.1 Psychological thera Banta 2016(1) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Gardner 2018(2) Mambi 2020-Arm1(1) Nambi 2020-Arm2(1) Samaogu 2000-Arm2(1) Gustaveson 2006(2) Heimma 2015 Meijer 2006(2) Meijer 2006(2) Weijer 2006(3) Yilmza 2017 Substotal (65% C1)	Mult Mean App + Exc 2.13 3.2 3.3 6.6 5.4 14 2.19 3.7 4 3.109 3.7 4 8.6 9.16 9.3 7.4 8.8 9.16 9.3 7.4 8.8 9.16 9.3 7.4 9.3 7.4 3.7 9.4 9.3 7.4 3.7 9.4 9.3 7.4 9.3 7.4 3.7 9.3 7.4 3.7 9.3 7.4 3.7 9.3 7.4 3.7 9.3 7.4 3.7 9.4 9.3 7.4 3.7 9.7 9.3 7.4 3.7 9.7 9.3 7.4 9.7 9.3 7.4 9.7 9.3 7.4 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7 9.7	< 0.000 = 0.03 ti-Model SD precise 4.2 6.8 4.36 4.36 2.76 3.18 3.18 3.278 3.18 3.18 3.272 c.000 ssive ssive 3.47 0.57 1.01 1.75 1.2 2.62	001) . df = : al Total vs. Ex 16 14 37 37 37 37 37 37 37 37 37 37	Uni Mean 1.5 0.92 0.5 24.34 30.67 19 24.34 30.67 12 (P < Passive -2.5 0.5 -0.5 0.5 1.66	99). P -Moda SD 8.3 4.5 5.34 4.3 2.68 2.58 2.58 2.68 2.58 2.63 2.78 3.02 0.0000 PT 1.67 2.87 3.26 3.	I Total 14 12 38 38 38 38 24 200 200 200 200 200 200 200	(d) Waight 4.2% 4.4% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8	Mean Difference IV Random. 95% Cf 0.63] - 4.18, 5.44] 0.31] - 4.07, 459 2.800 (54, 50, 61) 2.200 (54, 50, 61) 2.200 (54, 50, 61) 7.00 (26, 11, 139) 10.00 (83, 11, 17) 10.07 (83, 11, 17) 10.77 (5 100, 84, 11) 10.37 (17, 72, 21, 02) 18.11 (163, 0, 1922) 18.19 (522, 10, 16) 8.49 (560, 10, 29) 7.37 (5, 03, 16, 91) 1.50 (-0.56, 3.56) -2.50 (-4.40, -0.57) 1.50 (128, 172) 9.50 (814, 1166) 2.10 (10.44, 13.74) 12.00 (10.74, 14.41) 2.00 (10.74, 14.41)	Uni-Modal Multi-Modal Mean Difference
Test for suboroup difference Study or, Subprove 1.5.1 Psychological thera Bahat 2015(1) Bahat 2015(2) Barbat 2015(2) Garciner 2019(2) Garciner 2019(2) Garciner 2019(2) Javdanch 2020 Javdanch 2020 Javdanch 2020 Starcogiu 2020-Arm2(1) Nambi 2020-Arm2(1) Nambi 2020-Arm2(1) Starcogiu 2020-Arm2(1) Starcogiu 2020-Arm2(1) Garciares 2018(2) Gostavesna 2006(2) Heilminnen 2016(2) Heiger 2008(2) Meijer 2008(3) Meijer 2008(3) Meijer 2008(3) Meijer 2008(3) Meijer 2008(Mutr Mean app+ Exc 2.13 1.23 7.3 6.6 5.4 1.4 29 31.09 37.4 8.8 9.16 17; Ch ² = 5.51 (P - - 9.8 9.16 1.3 2 9.9 9.10 9.3 1.4 9.9 9.10 9.3 1.4 9.3 9.10 9.3 1.4 9.3 9.4 9.10 9.3 9.4 9.10 9.3 9.4 9.10 9.3 9.4 9.10 9.3 9.4 9.10 9.3 9.4 9.4 9.3 9.4 9.3 9.4 9.3 9.4 9.3 9.4 9.4 9.3 9.4 9.3 9.4 9.5 9.4 9.4 9.5 9.4 9.4 9.4 9.5 9.4 9.4 9.4 9.4 9.4 9.4 9.4 9.4 9.4 9.4	< 0.000 = 0.02 tl-Mod SD ercise 4.22 6.8 4.36 4.36 4.36 4.36 4.36 4.38 4.64 4.65 2.09 2.78 3.18 2.78 3.18 2.78 3.18 2.78 3.12 2.62 = 327.2 < 0.000 SD - 0.02 - 0	001) i. df = 3 al Total vs. Ex 16 17 37 37 37 37 37 37 37 37 37 3	Uni Mean 1.5 0.92 0.5 24.34 30.67 19 24.34 30.67 12 (P < Passive -2.5 0.5 -0.5 0.5 1.66	99). P -Moda SD 8.3 4.5 5.34 4.3 2.68 2.58 2.58 2.68 2.58 2.63 2.78 3.02 0.0000 PT 1.67 2.87 3.26 3.	I Total 14 12 38 38 38 38 24 200 200 200 200 200 200 200	(d) Waight 4.2% 4.4% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8% 4.8	Mean Difference IV Random. 95% Cf 0.63] - 4.18, 5.44] 0.31] - 4.07, 459 2.800 (54, 50, 61) 2.200 (54, 50, 61) 2.200 (54, 50, 61) 7.00 (26, 11, 139) 10.00 (83, 11, 17) 10.07 (83, 11, 17) 10.77 (5 100, 84, 11) 10.37 (17, 72, 21, 02) 18.11 (163, 0, 1922) 18.19 (522, 10, 16) 8.49 (560, 10, 29) 7.37 (5, 03, 16, 91) 1.50 (-0.56, 3.56) -2.50 (-4.40, -0.57) 1.50 (128, 172) 9.50 (814, 1166) 2.10 (10.44, 13.74) 12.00 (10.74, 14.41) 2.00 (10.74, 14.41)	Uni-Modal Multi-Modal Mean Difference
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Test for suborous difference Study or Suborous 1.5.1 Psychological thera Bahal 2015(1) Bahal 2015(2) Garciner 2019(2) Garciner 2019(2) Garciner 2019(2) Javdanch 2020 Javdanch 2020 Javdanch 2020 Javdanch 2020 Saracoglu 2020-Arm2(1) Nambi 2020-Arm2(1) Saracoglu 2020-Arm2(1) Saracoglu 2020-Arm2(1) Saracoglu 2020-Arm2(1) Guistro 2016(2) Velstofal (16% C) Helerogenety: Tauf = 214 Helminnen 2015(1) Meijer 2006(1) Meijer 2006(2) Meijer 2007(7) Subtofal (16% C) Heterogenety: Tauf = 30.17	Muti Mean upy+ Exc 2.13 1.23 7.3 8.123 7.3 7.3 7.3 7.4 8.8 9.16 ⁹ 9.16 ⁹ 9.7.6 ⁴ 9.7.6 ⁴ 9.7.6 ⁴ 9.7.6 ⁴ 9.7.6 ⁴ 1.2 3.3 7.4 8.8 9.7.6 ⁴ 1.2 3.7.3 7.4 8.8 9.1.6 ⁴ 1.2 3.7.4 8.8 9.1.6 ⁴ 1.2 3.7.4 8.7.4 8.7.4 8.8 9.1.6 ⁴ 1.2 3.7.4 8.7.4 8.8 9.1.6 ⁴ 1.2 3.7.4 8.8 9.1.6 ⁴ 1.2 3.7.4 8.8 9.1.6 ⁴ 1.2 3.7.4 8.8 9.1.6 ⁴ 1.2 3.7.4 8.8 9.1.6 ⁴ 1.2 3.7.4 8.8 9.1.6 ⁴ 1.2 3.2 7.4 8.8 9.1.6 ⁴ 1.2 3.2 7.4 8.8 9.1.6 ⁴ 1.2 3.2 7.4 8.8 9.1.6 ⁴ 1.2 3.2 7.4 8.8 9.1.6 ⁴ 1.2 3.2 7.4 8.8 9.1.6 ⁴ 1.2 3.2 7.4 8.8 9.1.6 ⁴ 1.2 3.2 7.4 8.8 9.1.6 ⁴ 1.2 3.2 7.4 8.8 9.1.6 ⁴ 1.2 3.2 9.8 8.2 9.1.0 9	ti-Mod SD ercise 4.2 6.8 4.36 4.64 4.65 2.09 3.18 3.48 3.18 3.42 2.6 8 3.18 3.42 2.6 8 3.18 3.42 2.6 3.18 3.42 2.6 8 3.18 3.42 2.6 8 5 4.26 5 5 4.26 5 5 5 5 7 5 7 5 7 5 7 5 7 5 7 5 7 5 7	01) df = 2 al Total vs. Ex 16 17 37 8 244 37 8 20 20 20 20 20 20 20 20 20 20	Uni Mean crcise 1.5 0.92 0.5 0.6 2.6 7 19.29 0.61 0.67 12 (P < Passive -0.5 0.5 0.5 0.5 0.5 1.66 6 (P < 1)	99). P 8.3 4.5 5.37 5.34 5.34 2.56 2.58 2.63 2.78 3.02 0.0000 PT 1.67 0.84 0.63 3.26 2.77 2.86 2.77 2.86 2.77 0.84 0.63 3.26 2.77 0.84 0.03 0.0000 Psych	I Total 14 12 38 38 8 20 200 200 200 200 200 200	(d) Weight 4 2% 4 4% 4 4% 4 4% 4 8% 4 8% 8 12% 9 96% 4 8% 4 8% 3 3.9%	Mean Difference IV. Random. 95% CI 0.63] -4.18, 5.44] 0.31 -4.07, 469] 6.80 -5.9, 9.01] 8.00 1.79, 2.21] 1.260 [D.54, 5.06] 7.00 [2.63, 11.17] 8.75 1.65, 5.61] 19.37 [1.77, 2.102] 8.41 [163, 11.82] 5.40 [636, 10.29] 7.97 [5.03, 10.91] 1.50 [-0.56, 3.56] 2.40 [1.26, 1.26] 7.97 [5.03, 10.91] 1.50 [-0.56, 3.56] 1.20 [12, 4, 72] 9.90 [814, 11.168] 1.20 (10.44, 13.58] 1.20 (10.44, 13.58] 1.20 (10.44, 13.58] 1.20 (10.44, 13.58] 1.20 (10.76, 14.44] 6.73 [2.06, 11.40]	Uni-Modal Multi-Modal Mean Difference
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(e) **Figure 4.** The forest plot of the subgroup analysis: (a) The subdivisions of different types of pain; (b) The subdivisions of different ranges of participants' mean age; (c) The subdivisions of different durations of treatments; (d) The subdivisions of different follow-up times; (e) The subdivisions of different types of physical therapy in control groups.

Outcome Subdivision	Subgroups	Statistics of Heterogeneity Test				95% CI of T ²		95% CI of I ²		Prediction Intervals	
Suburvision		df	Q	I ²	Tau ²	LL	UL	LL	UL	LL	UL
	CLBP	10	323.8	97%	29.62	3.63	5.37	79%	85%	0.00 *	21.29
Types of	CNP	6	181.84	97%	28.79	3.39	5.70	78%	85%	0.00 *	16.59
Pain	UEMD	2	4.02	50%	0.73	0 *	1.18	0% *	62%	0.00 *	26.55
	20-30	5	49.24	90%	2.71	0.39	1.02	56%	77%	6.14	18.38
Mean Age of	30-40	6	127.78	95%	5.34	0.70	1.28	73%	83%	0.14	14.10
Participants	40+	8	63.73	87%	0.61	0.10	0.24	53%	73%	1.01	7.05
	0–3 weeks	3	5.31	44%	0.58	0 *	0.98	0% *	57%	7.03	16.29
Duration of	4-6 weeks	11	1065.22	99%	45.64	3.73	4.74	89%	91%	0.00 *	23.12
Treatments	7–9 weeks	5	54.64	91%	13.68	1.95	4.86	59%	78%	0.00 *	14.31
	9+ weeks	1	2.39	58%	4.38	0 *	6.85	0%	69%	N/N	N/N
	0–12 weeks	14	965.81	99%	35.78	3.40	4.34	87%	89%	0.00*	20.28
Follow-up	13–24 weeks	6	380.24	98%	53.32	4.90	7.19	85%	89%	0.00 *	25.90
Times	24+ weeks	1	37.07	97%	13.05	1.02	3.15	74%	90%	N/N	N/N
Physical Therapy in	Active Exercise	12	327.26	96%	27.47	3.63	5.34	78%	84%	0.00 *	19.82
Control <u>Groups</u>	Passive Therapy	6	546.14	99%	39.00	3.13	4.36	88%	91%	0.00 *	23.27

Table 5. The result of heterogeneity test of subgroup analysis.

df: Degree of freedom; LL: Lower limit; UL: Upper limit; *: the true value is less than 0; CNP: Chronic neck pain; CLBP: Chronic low-back pain; UEMD: Upper extremity musculoskeletal disorders; N/N: when df = 1, the t-value could not be calculated so that the prediction intervals could not be estimated as well.

3.4.2. Meta-Regression

The large heterogeneity within the included studies made it necessary to do a meta-regression. The meta-regression made using STATA[®] 12 (StataCorp LLC, College Station, TX, USA), and the results can be seen in Figure 5 and Table 6.

The result of the meta-regression calculation for the covariate "follow-up times" showed that the proportion of the residual variation due to heterogeneity, which could be represented by the statistic "I-squared_res", was 99.58%. It meant that only 0.42% of the residual variation could be explained by between-study variance. And the result of the meta-regression calculation of the covariate "mean age of participants" showed that the proportion of the residual variation due to heterogeneity, which could be represented by the statistic "I²_{residual}" (I-squared_res), was 96.11%. It meant that only 3.89% of the residual variation could be explained by between-study variance. The proportion of the heterogeneity could be explained by between-study variance, which could be represented by the statistic "adjusted $R^{2''}$ (Adj R-squared), which was 33.10%. The result of the meta-regression calculation of the covariate "duration of treatments" showed that the proportion of the residual variation due to heterogeneity, which could be represented by the statistic "I²_{residual}" (I-squared_res), was 98.38%. It meant that only 1.62% of the residual variation could be explained by between-study variance. The proportion of the heterogeneity could be explained by between-study variance, which could be represented by the statistic "adjusted R²" (Adj R-squared), which was 14.46%. Lastly, the result of the Monte Carlo Permutation Test for Single Covariate of Meta-regression, the adjusted p-value changed from 0.139 to 0.008 to 1000 within the covariate "duration of treatments", "mean age of participants", and "follow-up times", indicating that there might not be the type I error existing within the included studies. The bubble chats of the results of the three covariates in the meta-regression.

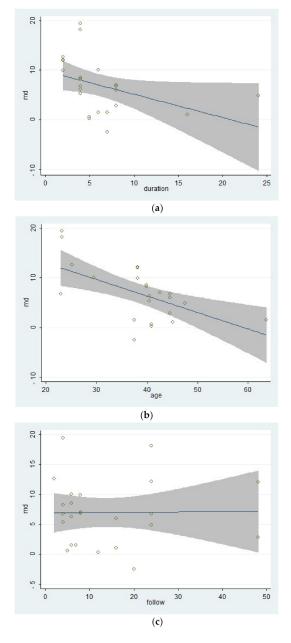


Figure 5. The bubble chats of the results of the three covariates in the meta-regression: (**a**) The duration of treatments; (**b**) Mean age of participants; (**c**) Follow-up times.

Table 6. Meta-regression result:	: The follow-up times and the SMD of effect.
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Meta-Regression									
Results			Covariate						
Item	Index	Duration of Treatments	Mean Age of Participants	Follow-Up Times (Week)					
Number of obs	Ν	24	24	24					
REML estimate of between-study variance	Tau ²	24.39	19.08	29.86					
% residual variation due to heterogeneity	I-squared_res	98.38%	96.11%	99.58%					
Proportion of between-study variance explained	Adj R-squared	14.46%	33.10%	-4.74%					
Statistical Significance	P-value	0.052	0.002	0.963					
Monte Carlo Permutation Test	Adjusted P-value	0.139	0.008	1.000					

3.4.3. Statistical Power

According to the result shown in Table 7, the meta-analysis's statistical power was higher than any included study. Moreover, the statistical power of the heterogeneity analysis was less than that of the pooled effect because of the interactions between the covariables. The result was consistent with the previous hypothesis.

Study	Statistical Power of Study	Subdivisions	Subgroups	Statistical Power of Effect Combination	Statistical Power of Heterogeneity Test
Gardner 2019 (1) [34]	13.45%		CLBP	100.00%	51.76%
Gardner 2019 (2)	18.34%	Types of Pain	CNP	48.92%	39.09%
Gardner 2019 (3)	8.15%		UEMD	100.00%	22.36%
Nambi 2020-Arm1 (1) [43]	5.62%	F 11	0-12 weeks	100.00%	61.90%
Nambi 2020-Arm1 (2)	11.75%	Follow-up	13-24 weeks	99.66%	39.09%
Nambi 2020-Arm2 (1)	17.54%	times	24+ weeks	48.16%	16.58%
Nambi 2020-Arm2 (2)	5.82%	Mean Age of	20-30	100.00%	35.41%
Saracoglu 2020-Arm1 (1) [40]	14.54%	Participants	30-40	99.99%	39.09%
Saracoglu 2020-Arm1 (2)	6.13%		40+	99.42%	45.79%
Saracoglu 2020-Arm2 (1)	5.61%	Physical	Active Exercise	100.00%	57.10%
Saracoglu 2020-Arm2 (2)	21.80%	Therapy in Control Groups	Passive Therapy	100.00%	39.09%
Gustavsson 2006 (1) [32]	19.81%	-	0–3 weeks	100.00%	27.16%
Gustavsson 2006 (2)	11.61%	Duration of	4–6 weeks	100.00%	54.51%
Javdaneh 2020 [42]	56.06%	Treatments	7–9 weeks	55.56%	35.41%
Ris 2016 [36]	64.57%		9+ weeks	14.78%	16.58%
Bahat 2015 (1) [33]	67.83%				
Bahat 2015 (2)	9.84%				
Tompson 2016 [37]	10.11%				
Yilmza 2017 [41]	7.36%				
Helminen 2015 [39]	9.19%	То	tal	100.00%	77.95%
Meijer 2006 (1) [35]	23.34%				
Meijer 2006 (2)	11.27%				
Meijer 2006 (3)	52.40%				
Gulsen 2020 [38]	27.89%				

Table 7. The result of statistical power test of all included studies and meta-analysis.

CNP: Chronic neck pain; CLBP: Chronic low-back pain; UEMD: Upper extremity musculoskeletal disorders.

4. Discussion

In this review, the fear-avoidance model of pain was used to explain the fear of physical movement following musculoskeletal disorders, and the clinic term "Kinesiophobia" was used to define and describe fear in relation to pain. Kinesiophobia could be acquired through personal experience or social learning and could be measured by the Tampa Scale of Kinesiophobia (TSK). Studies used the scores of TSK-17 as one of the outcomes and compared therapies combined multi-modal from both psychological and physical perspectives with therapies in uni-modal were included in this review to summarize the evidence that might support the application of multi-modal therapies for musculoskeletal disorders and the following pain.

Although a considerable heterogeneity within the included studies, the pooled effect was positive with a statistical significance, indicating that multi-modal therapies had an advantage over uni-modal therapies. High-quality evidence reported that a long-lasting multi-modal program was superior to the exercise program in reducing disability, fear-avoidance beliefs and pain, and enhancing the quality of life of patients with different kinds of pain [15]. The effects were clinically tangible and lasted for at least one year after the intervention ended [15,20,22].

The results of the subgroup analysis in the subdivision of different types of pain, which was showed in Figure 4a indicated that the multi-modal therapies were more used in the treatments for chronic pain in the people's trunk, especially in the neck and low back. This result was consistent with the previous fear-avoidance model about the fear of pain, which was that the experience of chronic, ongoing pain tends to become fear of pain [6,8]. What's more, multi-modal therapies combined

with physical therapies and psychological therapies had an advantage over therapies from a physical perspective, no matter the physical therapy was passive or active, as was showed in Figure 4e. Therefore, it was necessary to add psychological therapies in the treatments of chronic pain. A similar effect was found in studies that compared passive and active treatments for neck-shoulder pain and used the Visual Pain Scale (VAS) as an outcome measure [44]. Simultaneously, the age of participants, the duration of treatments, and the different follow-up times might affect the results. Within these factors, the participants' age was more likely to be taken into consideration since the pooled effects showed a decreasing trend with the increase of age in Figure 4b. According to the previous study results, older people were more often had a pain of longer duration, more frequently and of more complexity, felt more disabled, received more pain treatments and had more health problems, and often used passive coping for pain [45]. The influence of different durations of treatments seemed unclear, as was in Figure 4c. Perhaps there were few studies comparing different durations of treatments for pain or kinesiophobia, and each treatment protocol had a different optimal duration. It might result in low homogeneity among studies and poor goodness of fit of regression equations, as shown in Table 6. At last, the pooled effects at different follow-up times seemed stale, as was in Figure 4d, indicating that the effects of multi-modal therapies might clinically tangible and lasted for a long time [15,46].

According to the meta-regression results, the covariate "follow-up times" might not be the source of the heterogeneity because that different follow-up times of included studies could hardly explain the residual variation due to between-study variance [29]. On the contrary, the differences of mean age of participants and the duration of treatments could explain part of the between-study variance, meaning that the two covariates might be part of the sources of the heterogeneity and would affect the effects of therapies. What's more, the meta-regression of the mean age of participants had a significant statistical difference, showing that the effect of multi-modal therapies might decrease with age. This result might be related to the mental health and capacity of recovery of older adults [47,48]. Besides, the result of the meta-regression of the duration of treatments tended to be statistically significant. It indicated that there might be no additional benefit from increasing the duration of therapy for kinesiophobia. Finally, the goodness of fit of the model used in the meta-regression for these covariates was low, indicating that the results should be interpreted carefully.

A considerable heterogeneity within the included studies could be seen in the heterogeneity test in the meta-analysis and the subgroup analysis. The heterogeneity might come from the different designs of these studies. For example, the included studies had differences in the FITT characteristics (frequency, intensity, time, environments, and types) of the training plan [49,50]. Moreover, the different populations of the participants, the different blinding method, and some other factors, especially the different validities and reliability of the Tampa Scale of Kinesiophobia for participants with different educational backgrounds, culture, personalities, and types of musculoskeletal disorders [26,27,51], might lead a heterogeneity within studies.

This review had some limitations. Firstly, few studies reported the detailed pain duration of the participants or discussed the different effects between gender, leading it infeasible to make subgroup analysis or meta-regression for these covariates. Secondly, the statistical part of some studies did not consider the test-retest reliability of the Tampa Scale of Kinesiophobia, setting the test-retest reliability as 1.00 in their analysis of variance, which was impossible in a subjective questionnaire, so that the accuracy of their results was affected. Thirdly, in the search strategy, there might be an absence of data because the scores of the Tampa Scale of Kinesiophobia are usually reported as the secondary outcome. Finally, some studies didn't use the Tampa Scale of Kinesiophobia to measure the fear of physical movements.

The risk of bias was supposed to exist, and the source is various. For example, there were many musculoskeletal disorders that could lead to a fear of physical movements. Still, not all studies in the field of physical rehabilitation reported the score of the Tampa Scale of Kinesiophobia. In fact, to all kinds of musculoskeletal disorders with the following pain, the fear of physical movements was very common [1]. What's more, different shortened versions of the Tampa Scale of Kinesiophobia, such as

TSK-13 and TSK-11, were used in other studies [52,53], making these studies could not be included in the review. Lastly, other resources of publication bias could not be excluded [54–57].

The statistical power of all pooled effect analysis in this review was larger than that in any single primary study, subgroup analysis, and the heterogeneity test. This result accords with the statistical law of meta-analysis [29].

5. Conclusions

It could be concluded that (1) Although a large heterogeneity within the included studies existed, the multi-modal therapies had advantages over uni-modal therapies for kinesiophobia caused by musculoskeletal disorders with a medium effect size; (2) Multi-modal therapies were more used in the treatments for chronic pain in the people's trunk, especially in the neck and low back, and had an advantage over therapies from a physical perspective no matter the physical therapy was passive or active; (3) The effect of multi-modal therapies had a decreasing trend with the increase of age; (4) The influence of different durations of treatments seemed unclear; (5) The effects of multi-modal therapies might clinically tangible and lasted for a long time; (6) This review's statistical methods, which considered the test-retest reliability when combing psychological measurements data that usually output as a secondary outcome, were mathematically feasible.

Further researchers should pay more attention to rehabilitation from psychophysiology perspectives when dealing with musculoskeletal disorders. It was suggested to take the fear of physical movements as one of the main treatment targets and regard the improvement of pain-related indicators as one of the primary assessment criteria of treatment effectiveness. It might be necessary to provide standards and official guides of therapies for fear of pain following musculoskeletal disorders. For example, therapists could benefit from more data on the reliability and validity of the Tampa Scale of Kinesiphobia for different types of musculoskeletal disorders.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/24/9439/s1, Figure S1: The result of the GRADE assessment of evidence quality.

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References

- 1. Cimmino, M.A.; Ferrone, C.; Cutolo, M. Epidemiology of chronic musculoskeletal pain. *Best Pract. Res. Clin. Rheumatol.* **2011**, *25*, 173–183. [CrossRef]
- Vos, T.; Flaxman, A.D.; Naghavi, M.; Lozano, R.; Michaud, C.; Ezzati, M.; Shibuya, K.; Salomon, J.A.; Abdalla, S.; Aboyans, V.; et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012, 380, 2163–2196. [CrossRef]
- Artus, M.; Campbell, P.; Mallen, C.D.; Dunn, K.M.; van der Windt, D.A. Generic prognostic factors for musculoskeletal pain in primary care: A systematic review. *BMJ Open* 2017, 7, e012901. [CrossRef] [PubMed]
- 4. Keefe, F.J.; Rumble, M.E.; Scipio, C.D.; Giordano, L.A.; Perri, L.M. Psychological aspects of persistent pain: Current state of the science. *J. Pain* **2004**, *5*, 195–211. [CrossRef] [PubMed]
- 5. Turk, D.C.; Wilson, H.D. Fear of pain as a prognostic factor in chronic pain: Conceptual models, assessment, and treatment implications. *Curr. Pain Headache Rep.* **2010**, *14*, 88–95. [CrossRef]
- 6. Vlaeyen, J.W.; Linton, S.J. Fear-avoidance and its consequences in chronic musculoskeletal pain: A state of the art. *Pain* **2000**, *85*, 317–332. [CrossRef]

- 7. Leeuw, M.; Goossens, M.E.; Linton, S.J.; Crombez, G.; Boersma, K.; Vlaeyen, J.W. The fear-avoidance model of musculoskeletal pain: Current state of scientific evidence. *J. Behav. Med.* **2007**, *30*, 77–94. [CrossRef]
- 8. Vlaeyen, J.W.; Linton, S.J. Fear-avoidance model of chronic musculoskeletal pain: 12 years on. *Pain* **2012**, *153*, 1144–1147. [CrossRef]
- 9. Lundberg, M.; Grimby-Ekman, A.; Verbunt, J.; Simmonds, M.J. Pain-related fear: A critical review of the related measures. *Pain Res. Treat.* 2011, 2011, 494196. [CrossRef]
- 10. Kori, S.M.R.; Todd, D.D. Kinesiophobia: A new view of chronic pain behavior. Pain Manag. 1990, 3, 35–43.
- Meier, M.L.; Stampfli, P.; Vrana, A.; Humphreys, B.K.; Seifritz, E.; Hotz-Boendermaker, S. Fear avoidance beliefs in back pain-free subjects are reflected by amygdala-cingulate responses. *Front. Hum. Neurosci.* 2015, 9, 424. [CrossRef] [PubMed]
- Karos, K.; Meulders, A.; Gatzounis, R.; Seelen, H.A.M.; Geers, R.P.G.; Vlaeyen, J.W.S. Fear of pain changes movement: Motor behaviour following the acquisition of pain-related fear. *Eur. J. Pain* 2017, *21*, 1432–1442. [CrossRef] [PubMed]
- Roelofs, J.; Sluiter, J.K.; Frings-Dresen, M.H.; Goossens, M.; Thibault, P.; Boersma, K.; Vlaeyen, J.W. Fear of movement and (re)injury in chronic musculoskeletal pain: Evidence for an invariant two-factor model of the Tampa Scale for Kinesiophobia across pain diagnoses and Dutch, Swedish, and Canadian samples. *Pain* 2007, 131, 181–190. [CrossRef] [PubMed]
- 14. Lundberg, M.; Larsson, M.; Ostlund, H.; Styf, J. Kinesiophobia among patients with musculoskeletal pain in primary healthcare. *J. Rehabil. Med.* **2006**, *38*, 37–43. [CrossRef] [PubMed]
- 15. Monticone, M.; Ferrante, S.; Rocca, B.; Baiardi, P.; Farra, F.D.; Foti, C. Effect of a long-lasting multidisciplinary program on disability and fear-avoidance behaviors in patients with chronic low back pain: Results of a randomized controlled trial. *Clin. J. Pain* **2013**, *29*, 929–938. [CrossRef]
- 16. Barnhoorn, K.J.; Staal, J.B.; van Dongen, R.T.M.; Frölke, J.P.M.; Klomp, F.P.; van de Meent, H.; Samwel, H.; Nijhuis-van der Sanden, M.W.G. Are pain-related fears mediators for reducing disability and pain in patients with complex regional pain syndrome type 1? An explorative analysis on pain exposure physical therapy. *PLoS ONE* 2015, 10, e0123008. [CrossRef]
- 17. Wicksell, R.K.; Melin, L.; Lekander, M.; Olsson, G.L. Evaluating the effectiveness of exposure and acceptance strategies to improve functioning and quality of life in longstanding pediatric pain—A randomized controlled trial. *Pain* **2009**, *141*, 248–257. [CrossRef]
- Valenzuela-Pascual, F.; Molina, F.; Corbi, F.; Blanco-Blanco, J.; Gil, R.M.; Soler-Gonzalez, J. The influence of a biopsychosocial educational internet-based intervention on pain, dysfunction, quality of life, and pain cognition in chronic low back pain patients in primary care: A mixed methods approach. *BMC Med. Inform. Decis. Mak.* 2015, *15*, 97. [CrossRef]
- Klaassen, G.; Zelle, D.M.; Navis, G.J.; Dijkema, D.; Bemelman, F.J.; Bakker, S.J.L.; Corpeleijn, E. Lifestyle intervention to improve quality of life and prevent weight gain after renal transplantation: Design of the Active Care after Transplantation (ACT) randomized controlled trial. *BMC Nephrol.* 2017, *18*, 296. [CrossRef]
- Monticone, M.; Ambrosini, E.; Rocca, B.; Cazzaniga, D.; Liquori, V.; Pedrocchi, A.; Vernon, H. Group-based multi-modal exercises integrated with cognitive-behavioural therapy improve disability, pain and quality of life of subjects with chronic neck pain: A randomized controlled trial with one-year follow-up. *Clin. Rehabil.* 2017, 31, 742–752. [CrossRef]
- Monticone, M.; Ambrosini, E.; Rocca, B.; Magni, S.; Brivio, F.; Ferrante, S. A multidisciplinary rehabilitation programme improves disability, kinesiophobia and walking ability in subjects with chronic low back pain: Results of a randomised controlled pilot study. *Eur. Spine J.* 2014, 23, 2105–2113. [CrossRef] [PubMed]
- 22. Serrat, M.; Almirall, M.; Muste, M.; Sanabria-Mazo, J.P.; Feliu-Soler, A.; Mendez-Ulrich, J.L.; Luciano, J.V.; Sanz, A. Effectiveness of a multicomponent treatment for fibromyalgia based on pain neuroscience education, exercise therapy, psychological support, and nature exposure (NAT-FM): A pragmatic randomized controlled trial. J. Clin. Med. 2020, 9, 3348. [CrossRef]
- 23. Malfliet, A.P.M.; Van Oosterwijck, J.P.P.; Meeus, M.P.P.; Cagnie, B.P.P.; Danneels, L.P.P.; Dolphens, M.P.P.; Buyl, R.P.P.; Nijs, J.P.P. Kinesiophobia and maladaptive coping strategies prevent improvements in pain catastrophizing following pain neuroscience education in fibromyalgia/chronic fatigue syndrome: An explorative study. *Physiother. Theory Pract.* **2017**, *33*, 653–660. [CrossRef] [PubMed]

- 24. Trost, Z.; France, C.R.; Thomas, J.S. Examination of the photograph series of daily activities (PHODA) scale in chronic low back pain patients with high and low kinesiophobia. *Pain* **2009**, *141*, 276–282. [CrossRef] [PubMed]
- 25. Mari, K.E.; Lundberg, J.S.; Carlsson, S.G. A psychometric evaluation of the Tampa Scale for Kinesiophobia—From a physiotherapeutic perspective. *Physiother. Theory Pract.* **2004**, *20*, 121–133. [CrossRef]
- 26. Gomez-Perez, L.; Lopez-Martinez, A.E.; Ruiz-Parraga, G.T. Psychometric properties of the Spanish version of the Tampa Scale for Kinesiophobia (TSK). *J. Pain* **2011**, *12*, 425–435. [CrossRef] [PubMed]
- Koho, P.; Aho, S.; Kautiainen, H.; Pohjolainen, T.; Hurri, H. Test-retest reliability and comparability of paper and computer questionnaires for the Finnish version of the Tampa Scale of Kinesiophobia. *Physiotherapy* 2014, 100, 356–362. [CrossRef]
- Liberati, A.; Altman, D.G.; Tetzlaff, J.; Mulrow, C.; Gotzsche, P.C.; Ioannidis, J.P.; Clarke, M.; Devereaux, P.J.; Kleijnen, J.; Moher, D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *PLoS Med.* 2009, 6, e1000100. [CrossRef]
- 29. Borenstein, M.; Hedges, L.V.; Higgins, J.P.T.; Rothstein, H.R. *Introduction to Meta-Analysis*; John Wiley and Sons, Ltd.: Hoboken, NJ, USA, 2009.
- Higgins, J.P.T.; Green, S. (Eds.) Cochrane Handbook for Systematic, Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011. Available online: www.cochrane-handbook.org (accessed on 16 December 2020).
- 31. Atkins, D.; Eccles, M.; Flottorp, S.; Guyatt, G.H.; Henry, D.; Hill, S.; Liberati, A.; O'Connell, D.; Oxman, A.D.; Phillips, B.; et al. Systems for grading the quality of evidence and the strength of recommendations I: Critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv. Res.* 2004, 4, 38. [CrossRef]
- 32. Gustavsson, C.; von Koch, L. Applied relaxation in the treatment of long-lasting neck pain: A randomized controlled pilot study. *J. Rehabil. Med.* **2006**, *38*, 100–107. [CrossRef]
- Sarig Bahat, H.; Takasaki, H.; Chen, X.; Bet-Or, Y.; Treleaven, J. Cervical kinematic training with and without interactive VR training for chronic neck pain—A randomized clinical trial. *Man. Ther.* 2015, 20, 68–78. [CrossRef] [PubMed]
- 34. Gardner, T.; Refshauge, K.; McAuley, J.; Hübscher, M.; Goodall, S.; Smith, L. Combined education and patient-led goal setting intervention reduced chronic low back pain disability and intensity at 12 months: A randomised controlled trial. *Br. J. Sports Med.* **2019**, *53*, 1424–1431. [CrossRef] [PubMed]
- 35. Meijer, E.M.; Sluiter, J.K.; Heyma, A.; Sadiraj, K.; Frings-Dresen, M.H. Cost-effectiveness of multidisciplinary treatment in sick-listed patients with upper extremity musculoskeletal disorders: A randomized, controlled trial with one-year follow-up. *Int. Arch. Occup. Environ. Health* **2006**, *79*, 654–664. [CrossRef] [PubMed]
- 36. Ris, I.; Sogaard, K.; Gram, B.; Agerbo, K.; Boyle, E.; Juul-Kristensen, B. Does a combination of physical training, specific exercises and pain education improve health-related quality of life in patients with chronic neck pain? A randomised control trial with a 4-month follow up. *Man. Ther.* 2016, 26, 132–140. [CrossRef] [PubMed]
- Thompson, D.P.; Oldham, J.A.; Woby, S.R. Does adding cognitive-behavioural physiotherapy to exercise improve outcome in patients with chronic neck pain? A randomised controlled trial. *Physiotherapy* 2016, 102, 170–177. [CrossRef] [PubMed]
- 38. Gulsen, C.; Soke, F.; Eldemir, K.; Apaydin, Y.; Ozkul, C.; Guclu-Gunduz, A.; Akcali, D.T. Effect of fully immersive virtual reality treatment combined with exercise in fibromyalgia patients: A randomized controlled trial. *Assist. Technol.* **2020**, 1–8. [CrossRef]
- Helminen, E.-E.; Sinikallio, S.H.; Valjakka, A.L.; Vaisanen-Rouvali, R.H.; Arokoski, J.P.A. Effectiveness of a cognitive-behavioural group intervention for knee osteoarthritis pain: A randomized controlled trial. *Clin. Rehabil.* 2015, 29, 868–881. [CrossRef]
- 40. Saracoglu, I.; Arik, M.I.; Afsar, E.; Gokpinar, H.H. The effectiveness of pain neuroscience education combined with manual therapy and home exercise for chronic low back pain: A single-blind randomized controlled trial. *Physiother. Theory Pract.* **2020**, 1–11. [CrossRef]
- Yilmaz Yelvar, G.D.; Çırak, Y.; Dalkılınç, M.; Demir, Y.P.; Guner, Z.; Boydak, A. Is physiotherapy integrated virtual walking effective on pain, function, and kinesiophobia in patients with non-specific low-back pain? Randomised controlled trial. *Eur. Spine J.* 2017, *26*, 538–545. [CrossRef]

- 42. Javdaneh, N.; Letafatkar, A.; Shojaedin, S.; Hadadnezhad, M. Scapular exercise combined with cognitive functional therapy is more effective at reducing chronic neck pain and kinesiophobia than scapular exercise alone: A randomized controlled trial. *Clin. Rehabil.* **2020**. [CrossRef]
- 43. Nambi, G.; Abdelbasset, W.K.; Alrawaili, S.M.; Abodonya, A.M.; Saleh, A.K. Virtual reality or Isokinetic training; its effect on pain, kinesiophobia and serum stress hormones in chronic low back pain: A randomized controlled trial. *Technol. Health Care Off. J. Eur. Soc. Eng. Med.* **2020**. [CrossRef]
- 44. Savolainen, A.; Ahlberg, J.; Nummila, H.; Nissinen, M. Active or passive treatment for neck-shoulder pain in occupational health care? A randomized controlled trial. *Occup. Med.* **2004**, *54*, 422–424. [CrossRef] [PubMed]
- 45. Soares, J.J.; Sundin, O.; Grossi, G. The stress of musculoskeletal pain: A comparison between primary care patients in various ages. *J. Psychosom. Res.* **2004**, *56*, 297–305. [CrossRef]
- 46. Andersen, L.N.; Juul-Kristensen, B.; Sorensen, T.L.; Herborg, L.G.; Roessler, K.K.; Sogaard, K. Longer term follow-up on effects of Tailored Physical Activity or Chronic Pain Self-Management Programme on return-to-work: A randomized controlled trial. *J. Rehabil. Med.* **2016**, *48*, 887–892. [CrossRef] [PubMed]
- 47. Rothstein, J.M. The aged and the aging of physical therapy. *Phys. Ther.* **1992**, 72, 166–167. [CrossRef] [PubMed]
- 48. Gunther, R. Special problems of physical therapy in the aged. Z. Alternsforsch. 1986, 41, 323–330.
- 49. Helmhout, P.H.; Harts, C.C.; Staal, J.B.; Candel, M.J.; de Bie, R.A. Comparison of a high-intensity and a low-intensity lumbar extensor training program as minimal intervention treatment in low back pain: A randomized trial. *Eur. Spine J.* **2004**, *13*, 537–547. [CrossRef]
- 50. Heymans, M.W.; de Vet, H.C.; Bongers, P.M.; Knol, D.L.; Koes, B.W.; van Mechelen, W. The effectiveness of high-intensity versus low-intensity back schools in an occupational setting: A pragmatic randomized controlled trial. *Spine* **2006**, *31*, 1075–1082. [CrossRef]
- 51. La Touche, R.; Pardo-Montero, J.; Cuenca-Martinez, F.; Visscher, C.M.; Paris-Alemany, A.; Lopez-de-Uralde-Villanueva, I. Cross-cultural adaptation and psychometric properties of the Spanish version of the Tampa Scale for Kinesiophobia for temporomandibular disorders. *J. Clin. Med.* 2020, *9*, 2831. [CrossRef]
- 52. Steve, R.; Wobya, N.K.R.; Urmstona, M.; Watsond, P.J. Psychometric properties of the TSK-11: A shortened version of the Tampa Scale for Kinesiophobia. *Pain* **2005**, *117*, 137–144. [CrossRef]
- 53. Neblett, R.; Hartzell, M.M.; Mayer, T.G.; Bradford, E.M.; Gatchel, R.J. Establishing clinically meaningful severity levels for the Tampa Scale for Kinesiophobia (TSK-13). *Eur. J. Pain* **2016**, *20*, 701–710. [CrossRef] [PubMed]
- 54. Valiente-Castrillo, P.; Martín-Pintado-Zugasti, A.; Calvo-Lobo, C.; Beltran-Alacreu, H.; Fernández-Carnero, J. Effects of pain neuroscience education and dry needling for the management of patients with chronic myofascial neck pain: A randomized clinical trial. *Acupunct. Med. J. Br. Med Acupunct. Soc.* 2020. [CrossRef] [PubMed]
- 55. Simister, H.D.; Tkachuk, G.A.; Shay, B.L.; Vincent, N.; Pear, J.J.; Skrabek, R.Q. Randomized controlled trial of online acceptance and commitment therapy for fibromyalgia. *J. Pain* **2018**, *19*, 741–753. [CrossRef] [PubMed]
- 56. Turner, B.J.; Liang, Y.; Rodriguez, N.; Bobadilla, R.; Simmonds, M.J.; Yin, Z. Randomized trial of a low-literacy chronic pain self-management program: Analysis of secondary pain and psychological outcome measures. *J. Pain* **2018**, *19*, 1471–1479. [CrossRef]
- Miller, J.; MacDermid, J.C.; Walton, D.M.; Richardson, J. Chronic pain self-management support with pain science education and Exercise (COMMENCE) for people with chronic pain and multiple comorbidities: A randomized controlled trial. *Arch. Phys. Med. Rehabil.* 2020, 101, 750–761. [CrossRef]

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