"Robotic Assisted and Exoskeleton Gait Training Effect in Quality of Life and Psychosocial Factors to Upper Motor Neuron Disease Patients"

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Abstract

Purpose: REAGT has become the mainstream gait training module. Apart from the physical effects of REAGT, studies are investigating the psychosocial effects mostly as secondary outcomes. Our systematic review and meta-analysis aims to investigate the non-physical effects of REAGT in UMND patients. **Materials and methods:** We searched the databases for RCT studies fulfilling our inclusion criteria (stroke or spinal cord injury or multiple sclerosis patients undergoing REAGT). A meta-analysis of available assessment tools was conducted calculating the summary mean differences in two different timepoints, before and after the intervention using random-effects models. **Results:** The systematic search of the electronic databases identified 282 studies. 18 RCTs studies were considered eligible for data extraction and meta-analysis, according to our eligibility criteria. 19 different QoL and psychosocial assessment tools were documented and improved psychosocial effects in UMND patients (Time from Injury / Diagnosis: Stroke: 14 days – 30 months, SCI: 3.5 ± 2.1 months, MS if no relapse >3 months) were observed in all of them. All included studies provided information for a variety of outcomes. We were able to obtain adequate data to proceed with a ***quantitative synthesis*** for **QoL SF36 – MC (Mental Component), QoL SF36 – SF (Social Functioning), QoL SF36 – ER (Role Limitations due to Emotional Problems), QoL SF36 – GH (General Health Patients' Perspective), QoL SF36 – VT (Vitality), QoL SF36 – MH (Mental Health) and Fatigue Severity Scale (FSS). Conclusions:** There was a great variety of psychological assessment tools, used to evaluate the effects of REAGT in UMND patients. QoL SF36 – MH, depicting Mental Health's association to Quality of Life, seems to get improved after REAGT, since our meta-analysis of the data provided a statistically significant result. Although REAGT seems to have a positive psychosocial effect in patients with UMND, our meta-analysis could not deliver any more statistically significant results to the rest of the analysed data. Overall, REAGT seems to have a neutral or a positive effect to Quality of Life and other Psychosocial factors in patients with UMND.

Keywords: Exoskeleton, **Robotic-Assist*** (and all its derivatives), **Locomotor Train***(and all its derivatives), **Gait Train*** (and all its derivatives), **Walking Train***(and all its derivatives), **Spinal Cord Injur*** (and all its derivatives), **Stroke**, **Multiple Sclerosis**, **Quality of Life**, **Perception of Well Being**, **Sense of Well Being** and **Psychology** (and all its derivatives)

Introduction

Patients who suffered Spinal Cord Injury (SCI), survived a Stroke or living with Multiple Sclerosis (MS) have many symptoms, either common or unique for their condition. One of the most prevalent common symptom is the loss of motion. Both a Fast Walker[1] Stroke patient and a wheelchair user SCI or MS patient, all Upper Motor Neuron Lesions/Disease (UMND) patients set high in their rehabilitation priorities the improvement of their mobility/walking ability.

The correlation between motion and Quality of Life (QoL) seems obvious and it is established in previous research[2–5]. Thus, rehabilitation teams are usually focused on motion facilitating methods, techniques and technologies. Conventional physiotherapy with the variety of its modules and the use of tilt-tables was challenged (or enhanced) by Body-weight supported over-ground or treadmill walking training (BWSTT). BWSTT was challenged by Robotic-Assisted Gait Training (RAGT), which turned to be challenged by the use of Exoskeletons[6–8]. It seems very unlikely for any of the above-mentioned rehabilitation modalities to be obsolete since they all have their own advantages and drawbacks.

This unique rehabilitation variety, though, serves one purpose: the improvement of patients QoL and other psychosocial aspects in this life journey towards self-fulfillment and happiness after UMND. The aims of this systematic review and meta-analysis is to document the robotic-assisted and exoskeleton walking training protocols and methods and their effects in mental, social and cognitive QoL and other psychosocial factors.

Methods

This study was reported in accordance with PRISMA guidelines. Details of the protocol for this systematic review and meta-analysis were registered on PROSPERO (CRD42021255016) and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42021255016 .

Search strategy and Study selection

We systematically searched the following databases: Scopus, Pubmed, PEDro, Cochrane Trials (CENTRAL) library and DARE using as keywords the following: **Exoskeleton**, **Robotic-Assist*** (and all its derivatives), **Locomotor Train***(and all its derivatives), **Gait Train*** (and all its derivatives), **Walking Train***(and all its derivatives), **Spinal Cord Injur*** (and all its derivatives), **Stroke**, **Multiple Sclerosis**, **Quality of Life**, **Perception of Well Being**, **Sense of Well Being** and **Psychology** (and all its derivatives). We also hand-searched all the published data from unpublished research and references from review articles.

Two independent reviewers (VNC & AP) conducted the search. On the search results both reviewers applied the following criteria listed on the *table 1* (automatically using Rayyan (Rayyan Systems, Inc.), if possible or manually):

Inclusion Criteria	Exclusion Criteria
Journals	Books, Editorials, Expert Opinions
Clinical Trials and RCTs	Reviews and Meta-analysis
Human Studies	Non-Human Studies
Publishing Date ≥ 2011	Publishing Date < 2011
English Language	Non-English Language

SCI, Stroke or Multiple Sclerosis studies	Tumor, Brain Injury, Parkinson's disease studies
Robotic or Exoskeleton produced Walking Training	Overground, BWSTT, Parallel Bars, and other Physical Therapy Methods (unless they are used as comparison/control groups)

table 1: Article inclusion and exclusion criteria

In cases where there was a disagreement whether to include or exclude an article to/from the systematic review, meetings were held with the "Megatron" team of researchers. All disagreement cases were resolved on a mutual consensus.

The risk of bias assessment was performed by utilizing quality questions relevant to the included studies from the RoB 2 tool: A revised Cochrane risk of bias tool for randomized trials[9].

Data Extraction

From each eligible study, we extracted information about the study design, the intervention protocol, the QoL and/or other Psychosocial assessment tools used. We stratified the studies according to the patients' UMND, the walking training equipment used, the assessment tool(s) used and the total intervention time.

We extracted information on all measurements from any time frame (Baseline, After Intervention and Follow-up(s)), made with QoL and/or other psychosocial assessment tools. These assessment tools (questionnaires, forms, indexes or scales) were used, after given instructions, by the patients or for the patients, in case of writing inability, by close relatives or assessors involved in the study.

Quantitative Synthesis and Analysis

We calculated the standardised summary mean differences along with the corresponding 95% confidence intervals (CIs), for a variety of QoL and/or psychosocial assessment tools (questionnaires, forms, indexes or scales), for the group of participants that undertook the REAGT, compared to the control group. The summary mean differences were calculated by pooling the study specific estimates using random-effects models[10], and in two different time points; once before and then after the treatment. The presence of heterogeneity was estimated with the Cochran's Q statistic and it was quantified with I^2 [11]. All analyses were performed using Stata (version 14; StataCorp, College Station, TX, USA).

Results

Study Selection

Searching the electronic databases, we found 282 articles. Of this total, 34 articles were excluded because they were duplicates, and another 1 article was excluded due to lack of access to the full text. Of the 247 remaining articles, 229 were excluded because they lacked one or more inclusion criteria (*figure 1*). Finally, 18 articles were included in the systematic review of which 8 provided the comparable data to be included in the quantitative synthesis and analysis. The characteristics of the studies are listed in table 1.

Presentation of the articles

According to the study design

All eligible studies[4,12–28] had a patients' randomisation process in their design according to our inclusion criteria. Thirteen authors described their study as a "Control study"[4,12,16,18–26,28], three as a "Clinical study"[13,15,17] and one as an "Open-Labeled evaluation"[27]. Five studies are described as "Prospective" [4,14,19,21,27]. Five studies are described, in the article title or the "Methodology" section as "Pilot"[15,17,18,20,21], while two others describe their results as "Preliminary"[12,13]. All studies, except one[17], put effort to keep the studied groups homogenous and/or similar in population. Finally, one of the studies is a "Crossover study"[22] and on is a "Multicenter study"[23].

According to the study population

As described, all studies enrolled UNMD patients. Nine studies enrolled MS patients[12,13,16,18,21–24,26], eight studies enrolled stroke survivors[4,15,17,19,20,25,27,28] and one enrolled SCI patients[14].

Two studies enrolled <20 patients to their study[18,20]. The one study with the crossover design enrolled 19 patients[22]. 20-40 patients were enrolled in ten studies[4,12–16,21,25,27,28]. There was a study, comparing three groups, that enrolled 51 patients[19]. Three studies enrolled 41-60 patients[17,23,26] and, finally, one study enrolled 72 patients[24].

According to intervention

Sixteen studies utilized Robotic or Electromechanical - Assisted Gait Training (RAGT or EAGT, respectively)[4,13,14,16–28]. Specifically, ten studies used a Locomat®-Hocoma [13,14,17,19,21–26], two studies used Walkbot®-P&S Mechanics[4,20], one study used HAL®-Kawamoto[27], one study used Gait Trainer GT1-Reha Stim[16], one study used G-EO System™-Reha Technology[18] and one study used a custom made[28] walking training apparatus respectively. Finally, two studies used Ekso™-Ekso Biononics[12,15] exoskeleton for walking training.

REAGT intervention time was calculated in minutes for simplicity, since frequency of interventions per week and time period where the interventions occurred, varied greatly. Eight studies used REAGT for <500'[3,5,8,10,11,13,14,16], six studies used REAGT for 500'-1000'[1,6,9,15,17,18], one study used REAGT for 1440'[4], two studies used REAGT for 1600'[2,7] and finally one study used REAGT for 2250'[12].

The results of the "intervention group" were compared with the results of the "control group". As expected, the "control group" was subjected to a more "conventional" therapeutic approach. Since best clinical practice for treating UNMD patients differs in national health systems, "conventional" can have various meanings, although in every included study, except one[19], an effort was made for the "intervention" and the "control" group to be subjected to similar therapeutic time. Underlining the above, ten studies compared Conventional Physical Therapy (CPT) and REAGT with CPT and Overground Walking Training (OWT)[4,12,14,15,19,20,22,24–26], two studies compared REAGT with OWT giving no details for any other treatments to their subjects during the study time period[21,23], one study compares REAGT with CPT giving no details for included OWT[27] and one study compares REAGT with Sensory Integration Balance Training (SIBT)[16]. Two studies compared REAGT with and without Virtual Reality (VR) enhancement while their subjects received the same CPT[13,17] while one study with same comparison groups advised their subjects to refrain from any other treatment[18]. Finally, one study compared the assistance to the resistance effects of the same (custom-made) REAGT system to its population[28].

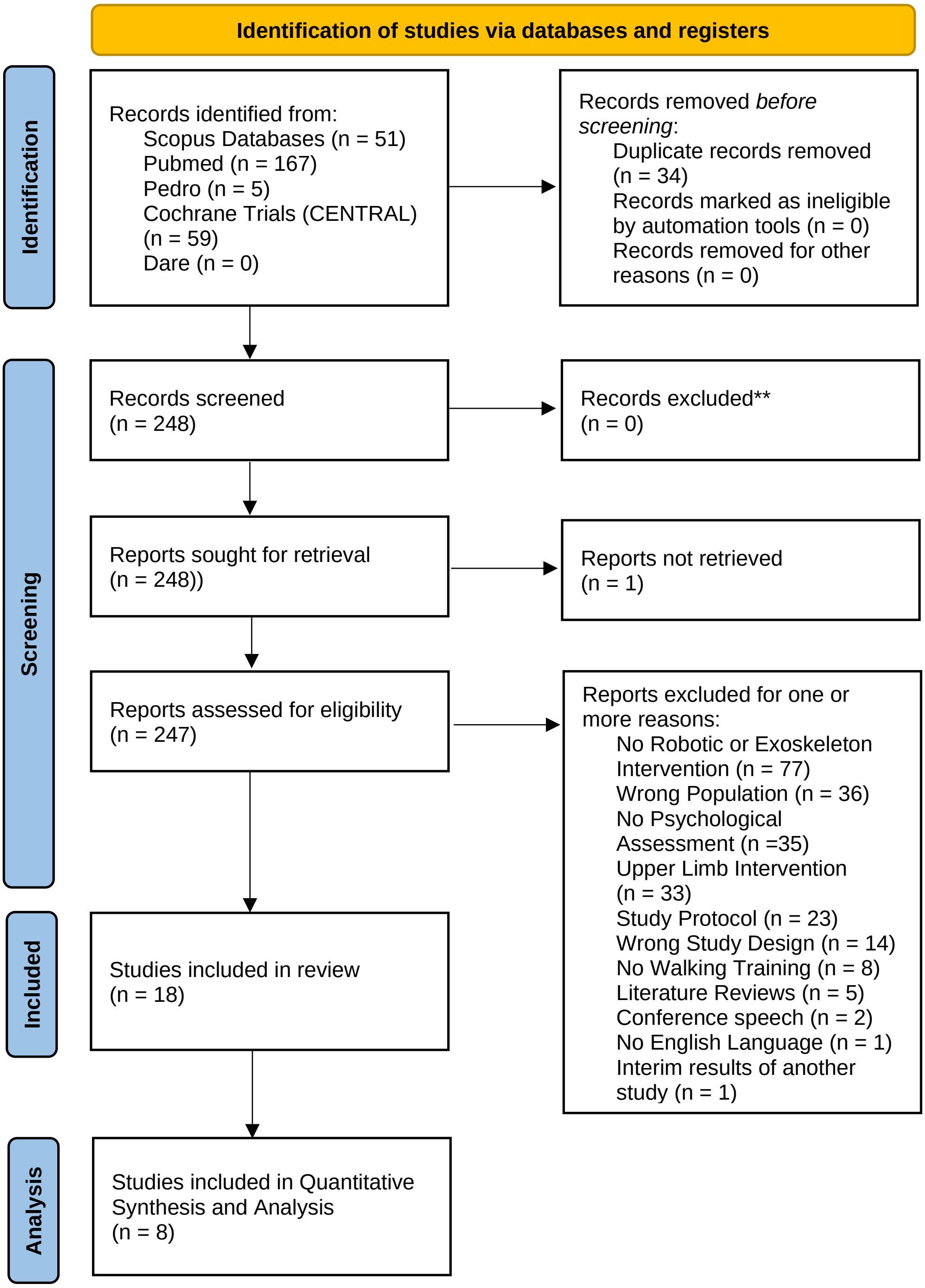

figure 1: Flow diagram of the study selection procedure.

According to assessment tools

We recorded a great collection of different psychosocial assessment tools: QoL was assessed by either the Short Form-12[29] (SF-12) or the Short Form-36[30] (SF-36). Using the SF-12, psychosocial and mental conditions were assessed by the Mental Health Component Scale[31] (MCS-12). Using the Short Form-36, psychosocial and mental conditions were assessed by either the Mental Component Summary[32,33] (MCS-36 or QoL SF-36 – MC) or by the various components as are. Both Mental Component Summaries, in general, are the summaries of the various QoL questionnaire components with a relative contribution to the Summary, depending to their correlation with psychosocial and mental conditions. Differences in scoring algorithms (such as RAND) that were found in our review, seem to have minor statistical effects[34,35]. Clarifying these details, QoL assessments were made with the MCS-12, the MCS-36, and the SF-36 subcomponents for Social Functioning (SF), Role limitations due to Emotional problems (ER), General Health patients' perspective (GH) and Vitality (VT).

Alongside with these, QoL assessments were made with the EuroQoL-5 Dimension[36] (EQ-5D), with the Stroke Specific Quality of Life scale[37] (SS-QOL) and, deriving from the Multiple Sclerosis Quality of Life-54 (MSQOL-54), the MSQOL-54 Mental Health Composite summary[38] (MSQOL-54-MHC).

Other psychosocial assessment tools that were used are: the Beck Depression Inventory[39] (BDI), the Beck Depression Inventory II[40] (BDI-II), the Body Esteem Scale[41] (BES), the Body Uneasiness Test[42] (BUT) with its two subtests and multiple parts, the COPE[43,44] inventory with its five scales, the Fatigue Severity Scale[45] (FSS), the General Well-Being Schedule[46] (specifically, the 17th Visual Analogue Scale (VAS) question)(GWBS q.17), the Hamilton Rating Scale for Depression[47] (HRSD), the Modified Fatigue Impact Scale[48] (the Psychosocial part)(MFIS-Psychosocial), the Psychological Component of the Multiple Sclerosis Impact Scale[49] (MSIS-29-PC), the Patient Health Questionnaire[50] (PHQ-9), the Psychological General Well-Being Index[51] (PGWBI) with its six parts, and the Stroke Impact Scale[52] (specifically the 8th domain)(SIS d.8)

QoL and psychosocial assessment tools were, usually, used to extract secondary outcomes along with mobility and functionality assessment tools. The majority of the studies used one[4,12,14,18–22,25,27,28] or two[13,16,26], but there were some studies, oriented more to the QoL and psychosocial effects of REAGT, that used three[23] or four[15,17,24] assessment tools.

In total, seven studies[14,21–25,28] used QoL SF-36, either by reporting results from QoL SF36 – MC or by any other subscale. Three studies[16,23,24] used FSS. The results of these studies were adequate to proceed with a quantitative synthesis. All other assessment tools were used in two (EQ-5D[4,26], MSQOL-54-MHC[16,18], COPE[13,15], HRSD[13,15] and PHQ-9[23,24]) or one (MCS-12[17], SS-QOL[19], BDI[17], BDI-II[20], BES[17], BUT[17], GWBS q.17[26], MFIS-Psychosocial[12], MSIS-29-PC[24], PGWBI[15] and SIS d.8[27]) studies. The recorded results of these assessments are listed in Appendix 01.

Results of syntheses

All included studies provided information for a variety of outcomes. We were able to obtain adequate data to proceed with a quantitative synthesis for MCS-36 (QoL SF-36-MC), QoL SF-36 – SF (Social Functioning), QoL SF-36 – ER (Role Limitations due to Emotional Problems), QoL SF-36 – GH (General Health Patients' Perspective), QoL SF36 – VT (Vitality), QoL SF36 – MH (Mental Health) and FSS (Fatigue Severity Scale).

Five studies reported results on MCS-36[21–24,28]. Overall, no statistically significant differences were observed between the two groups of participants on the mean MCS-36 for both time-point measurements (before intervention: summary mean difference: -0.40; 95% CI: -2.62, 1.80, *figure 1A*; post intervention: summary mean difference: 1.67; 95% CI: -1.03, 4.38 *figure 1B*); small heterogeneity observed (I^2 = 0%, I^2 = 18.6% respectively).

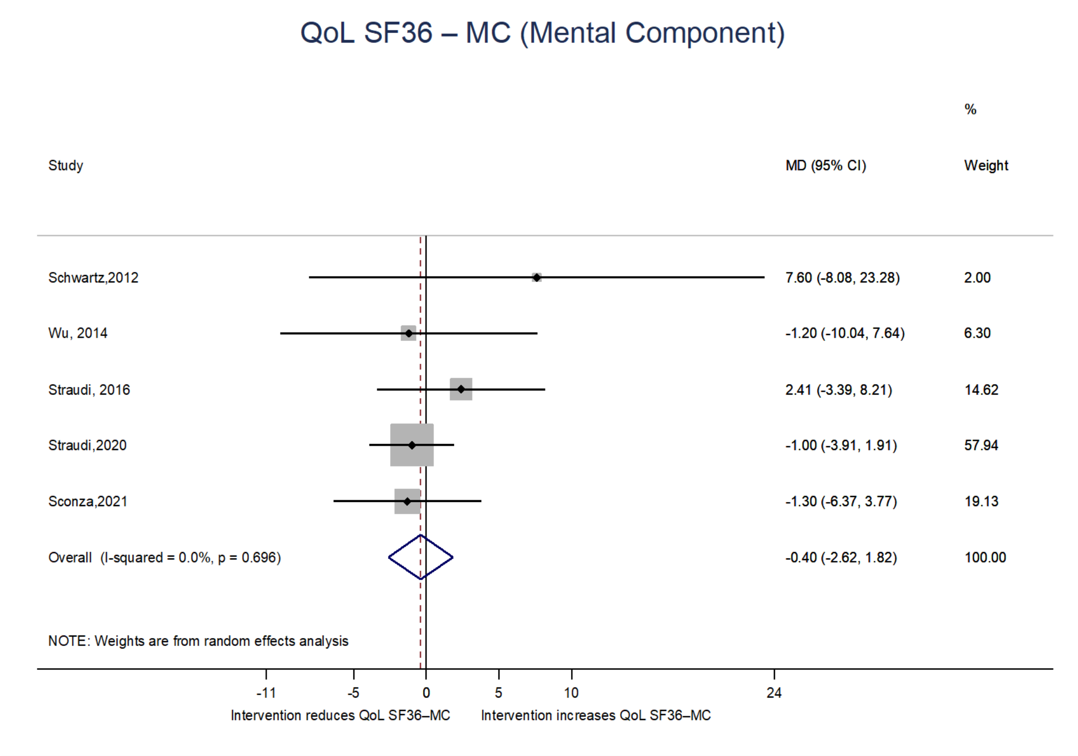

figure 1A: Pre-intervention MCS-36

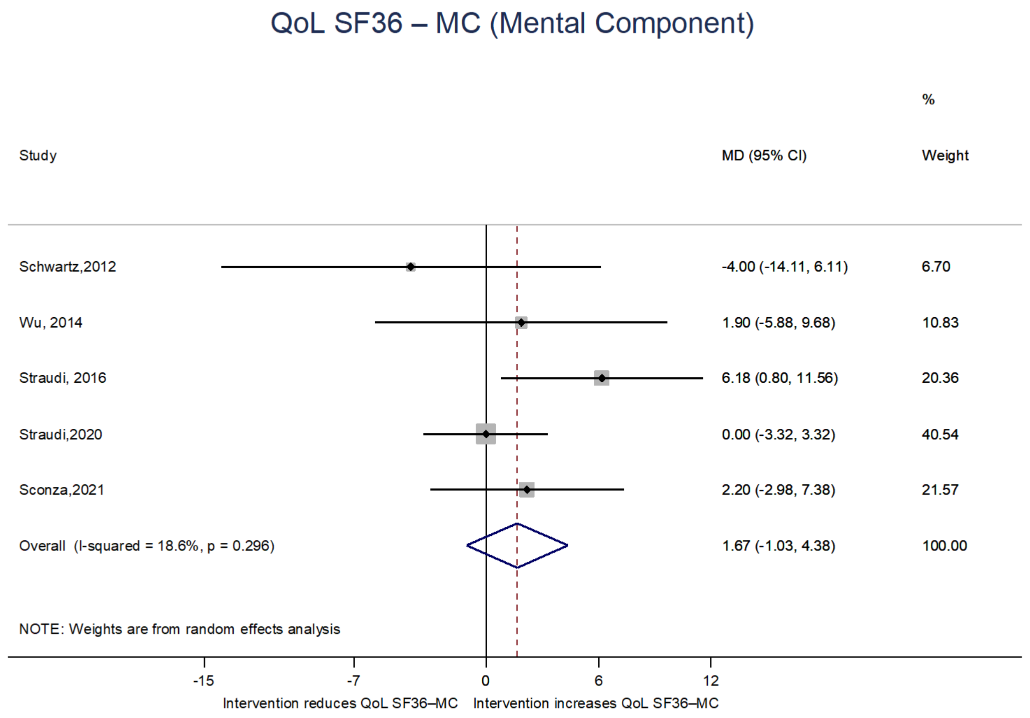

figure 1B: Post intervention MCS-36

Four studies reported results on QoL SF-36 – SF (Social Functioning)[14,23–25]. Overall, no statistically significant differences were observed between the two groups of participants on the mean QoL SF-36 – SF for both time-point measurements (before intervention: summary mean difference: 1.85; 95% CI: -3.20, 6.90, *figure 2A*; post intervention: summary mean difference: 2.99; 95% CI: -7.48, 13.45 *figure 2B*); no-heterogeneity was observed before (I^2 = 0%) and large heterogeneity was observed after the intervention (I^2 = 60.5%).

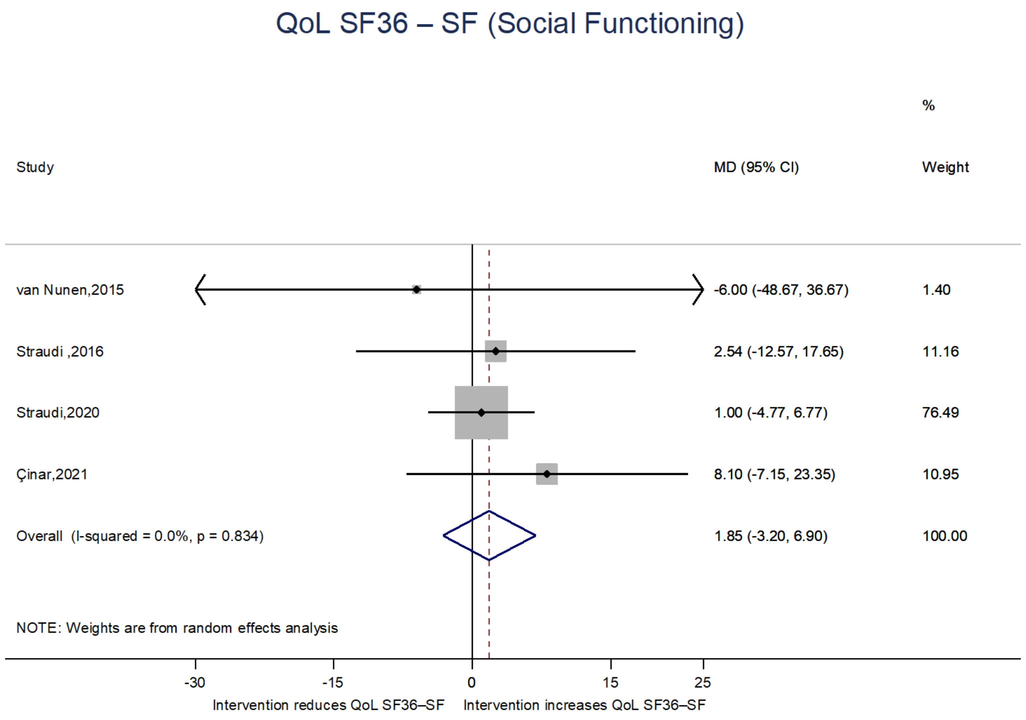

figure 2A: Pre-intervention QoL SF-36-SF

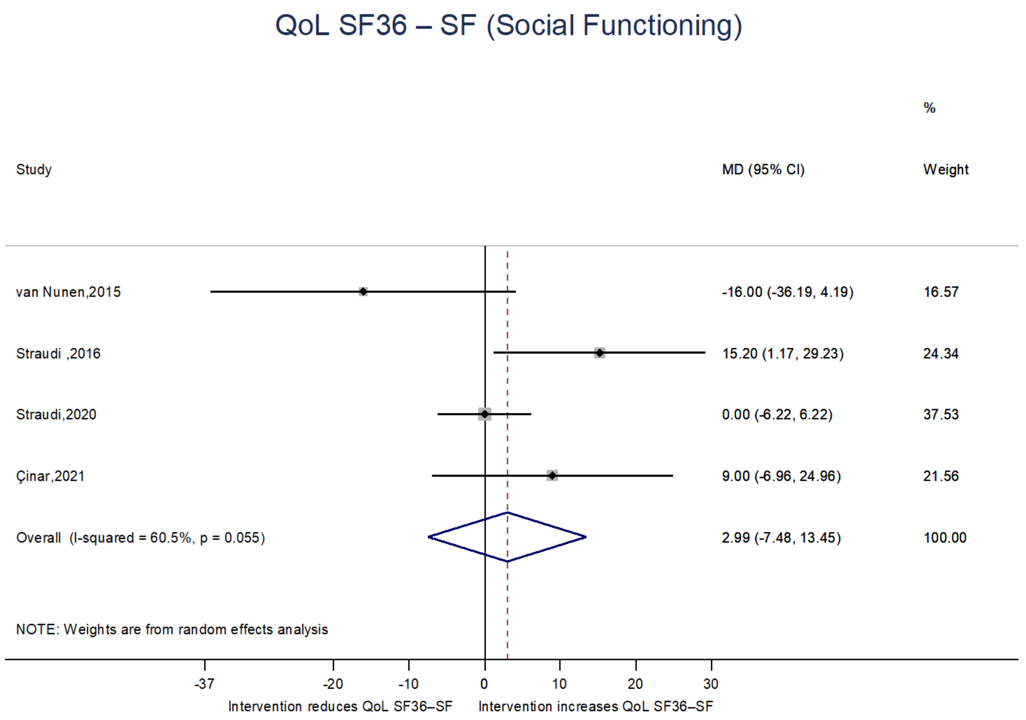

figure 2A: Post intervention QoL SF-36-SF

Three studies reported results on QoL SF36 – ER (Role Limitations due to Emotional Problems)[14,23,24]. Overall, no statistically significant differences were observed between the two groups of participants on the mean QoL SF36 – ER for both time-point measurements (before intervention: summary mean difference: 3.04; 95% CI: -5.51, 11.59, *figure 3A*; post intervention: summary mean difference: 7.72; 95% CI: -5.04, 20.48 *figure 3B*); no-heterogeneity was observed before ($I^2 = 0\%$) and small heterogeneity was observed after the intervention ($I^2 = 29\%$).

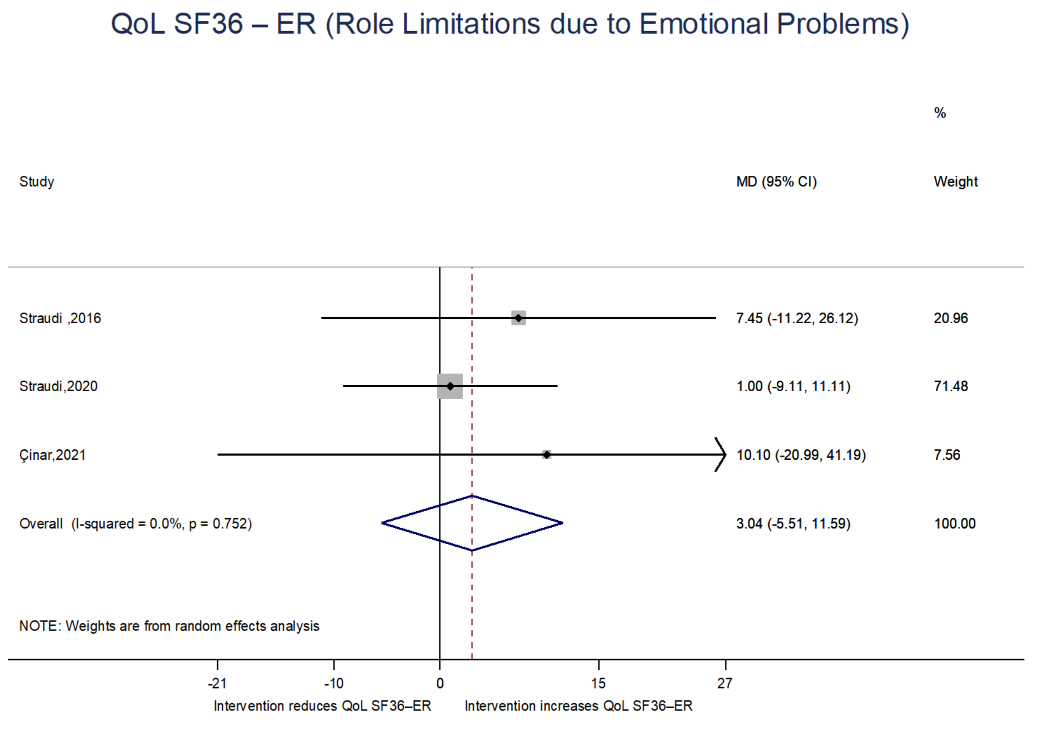

figure 3A: Pre-intervention QoL SF-36-ER

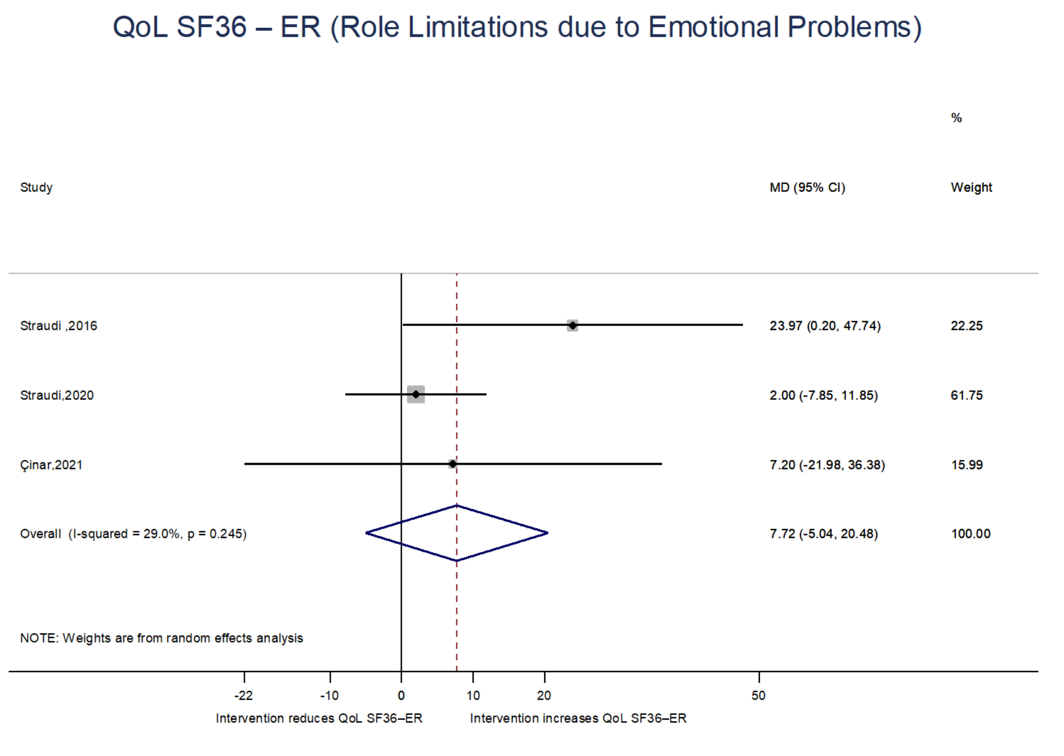

figure 3A: Post intervention QoL SF-36-ER

Four studies reported results on QoL SF36 – GH (General Health Patients' Perspective)[14,24,24,25]. Overall, no statistically significant differences were observed between the two groups of participants on the mean QoL SF36 – GH for both time-point measurements (before intervention: summary mean difference: 0.55; 95% CI: -3.39, 4.49, *figure 4A*; post intervention: summary mean difference: 2.30; 95% CI: -6.23, 10.84 *figure 4B*); no-heterogeneity was observed before (I^2 = 0%) and large heterogeneity was observed after the intervention (I^2 = 67%).

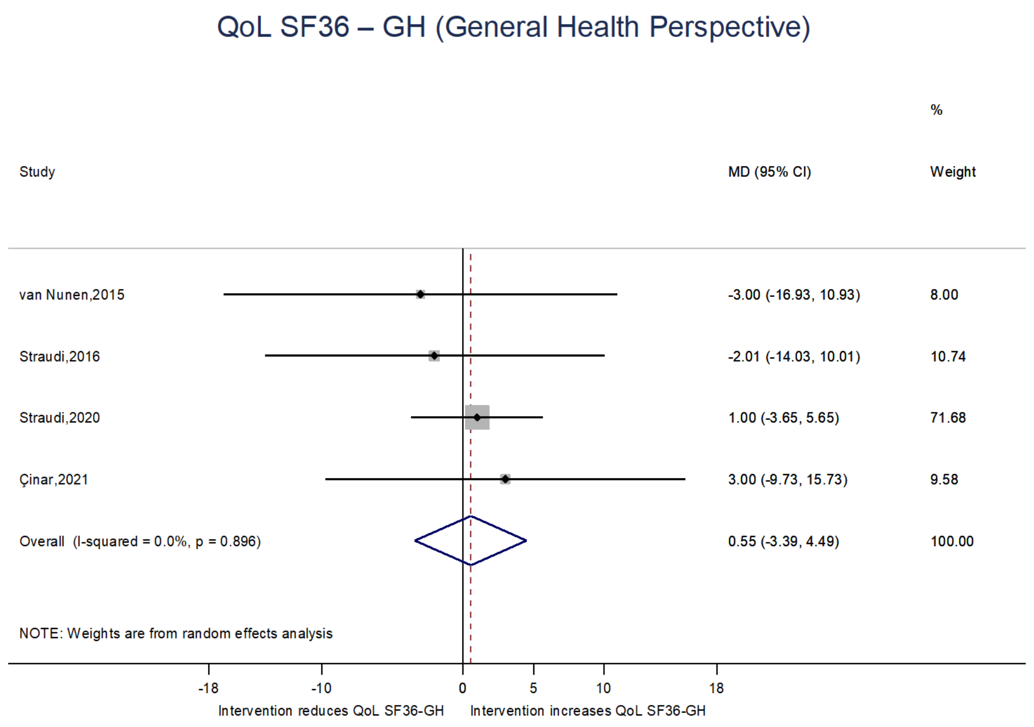

figure 4A: Pre-intervention QoL SF-36-GH

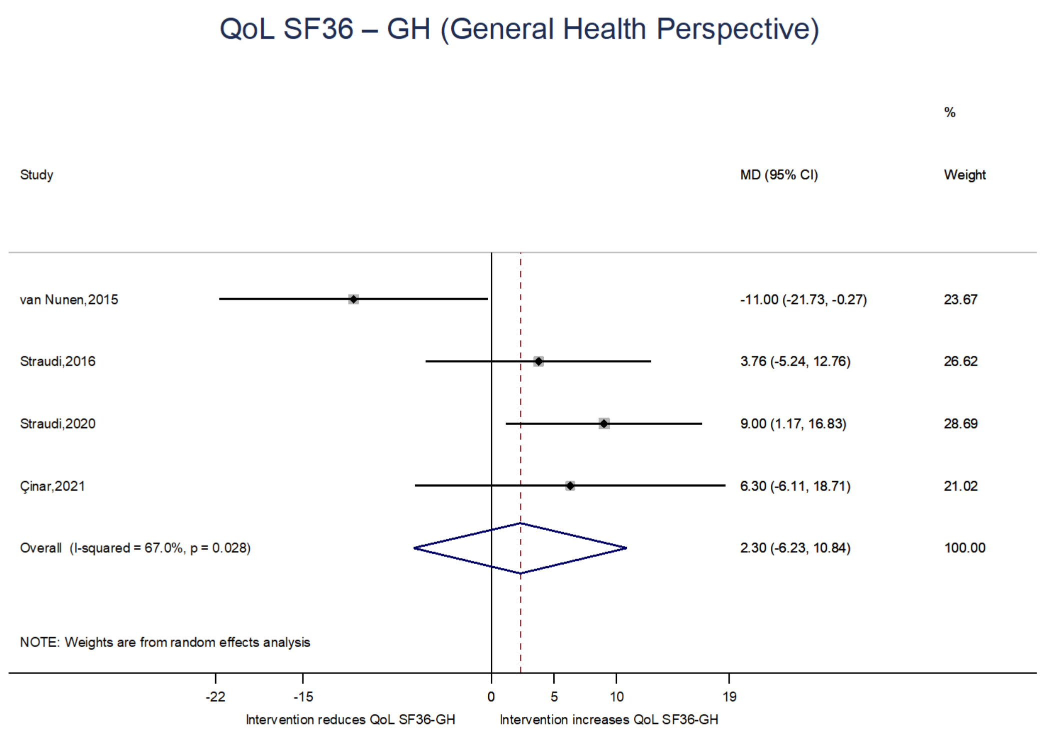

figure 4B: Post intervention QoL SF-36-GH

Three studies reported results on QoL SF36 – VT (Vitality)[14,23,24]. Overall, no statistically significant differences were observed between the two groups of participants on the mean QoL SF36 – VT for both time-point measurements (before intervention: summary mean difference: -2.43; 95% CI: -6.88, 2.02, *figure 5A*; post intervention: summary mean difference: 0.69; 95% CI: -6.42, 7.79 *figure 5B*); no-heterogeneity was observed before (I^2 = 0%) and medium heterogeneity was observed after the intervention (I^2 = 50.1%).

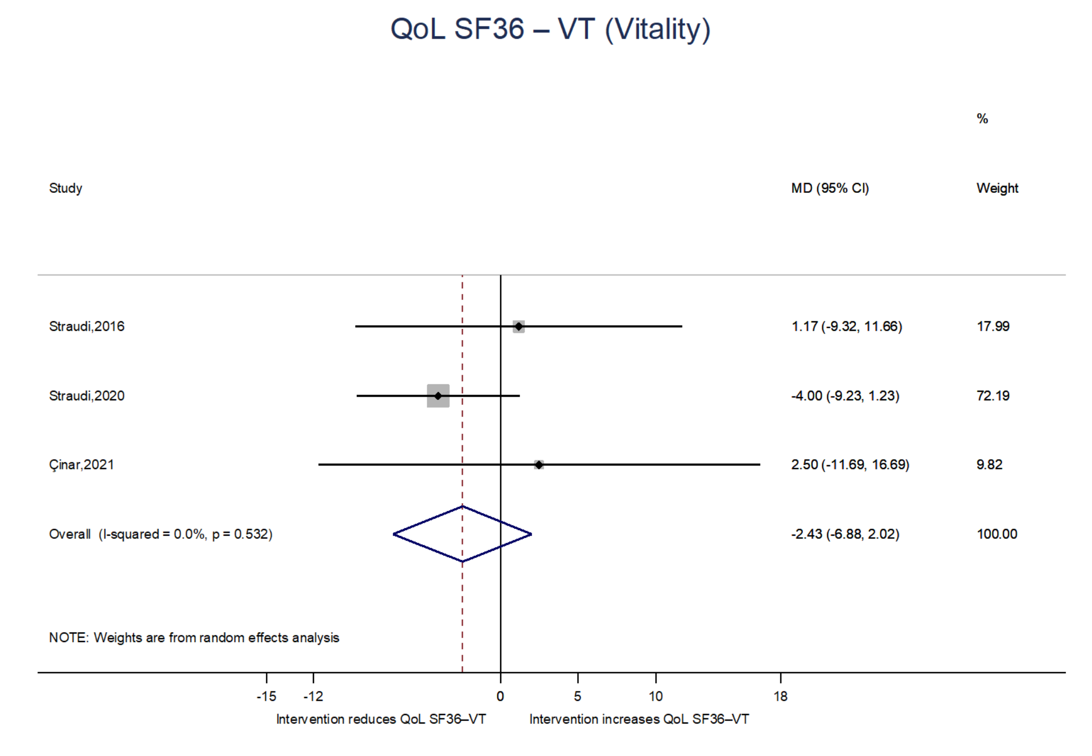

figure 5A: Pre-intervention QoL SF-36-VT

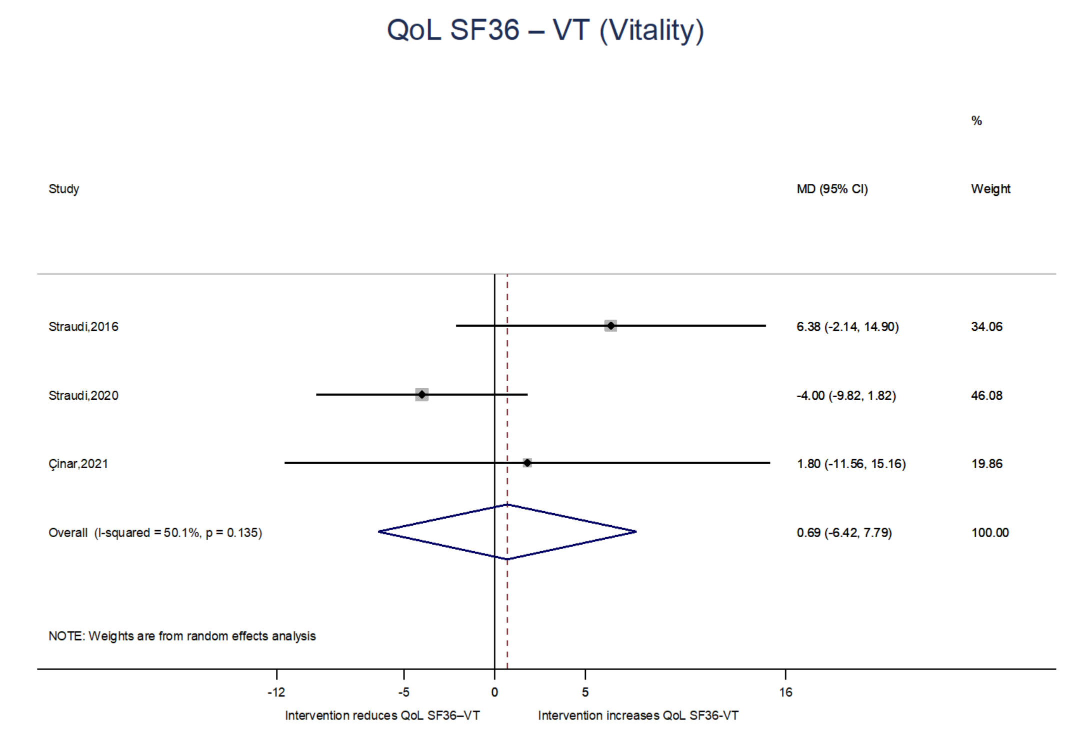

figure 5B: Post intervention QoL SF-36-VT

Three studies reported results on FSS[16,23,24]. Overall, no statistically significant differences were observed between the two groups of participants on the mean FSS for both time-point measurements (before intervention: summary mean difference: 0.26; 95% CI: -0.03, 0.55, *figure 6A*; post intervention: summary mean difference: 0.12; 95% CI: -0.28, 0.51 *figure 6B*); no-heterogeneity was observed before (I^2 = 0%) and small heterogeneity was observed after the intervention (I^2 = 25.8%).

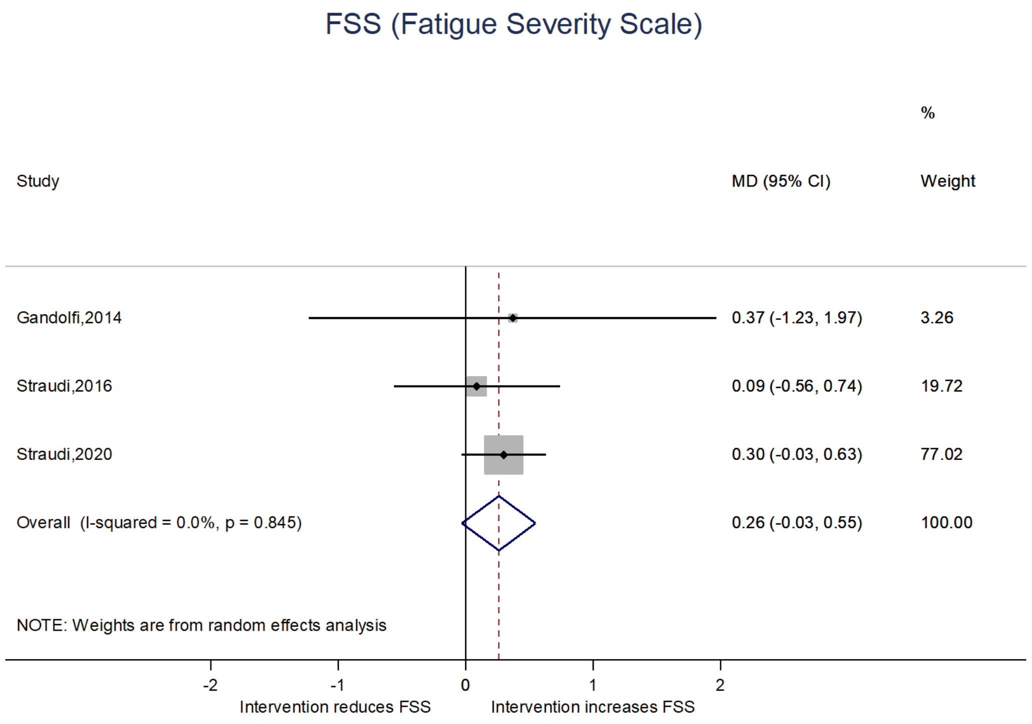

figure 6A: Pre-intervention FSS

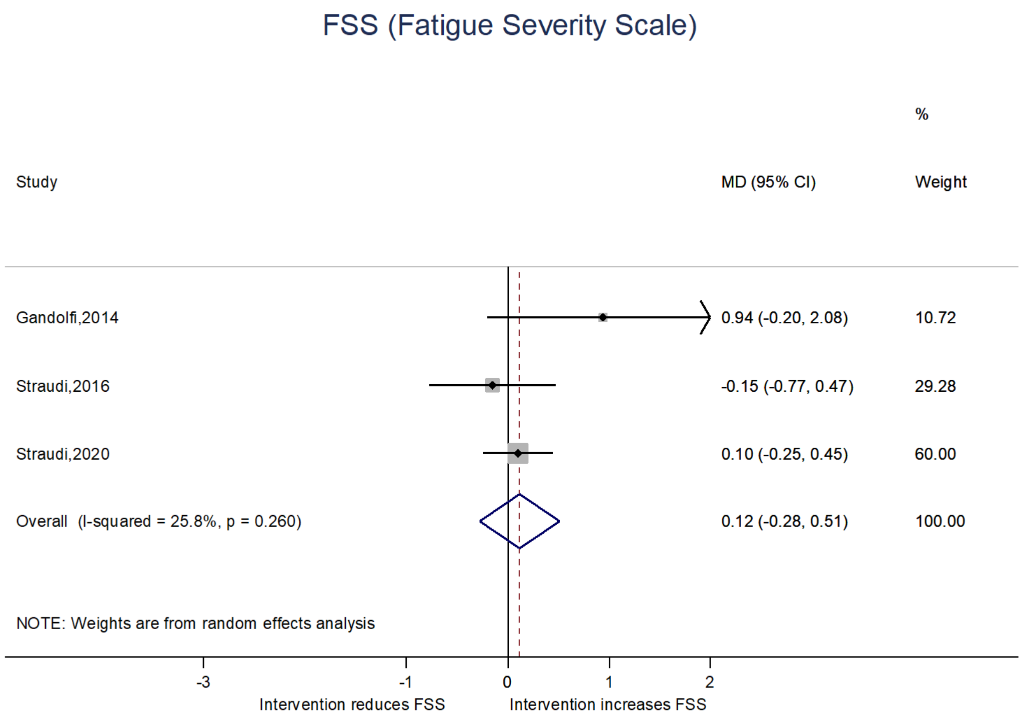

figure 6B: Post intervention FSS

Finally, three studies reported results on QoL SF36 – MH (Mental Health). A non-significant difference between the two groups of participants was observed on the pre-intervention time point (summary mean difference: 0.26; 95% CI: -0.03, 0.55, *figure 7A*) with no heterogeneity observed (I^2 = 0%). However, after the intervention a statistically significant difference of 6.51 units was observed from the group that received it, compared to the other group (CI: 3.07, 9.95, *figure 7B*), with no heterogeneity observed (I^2 = 0%).

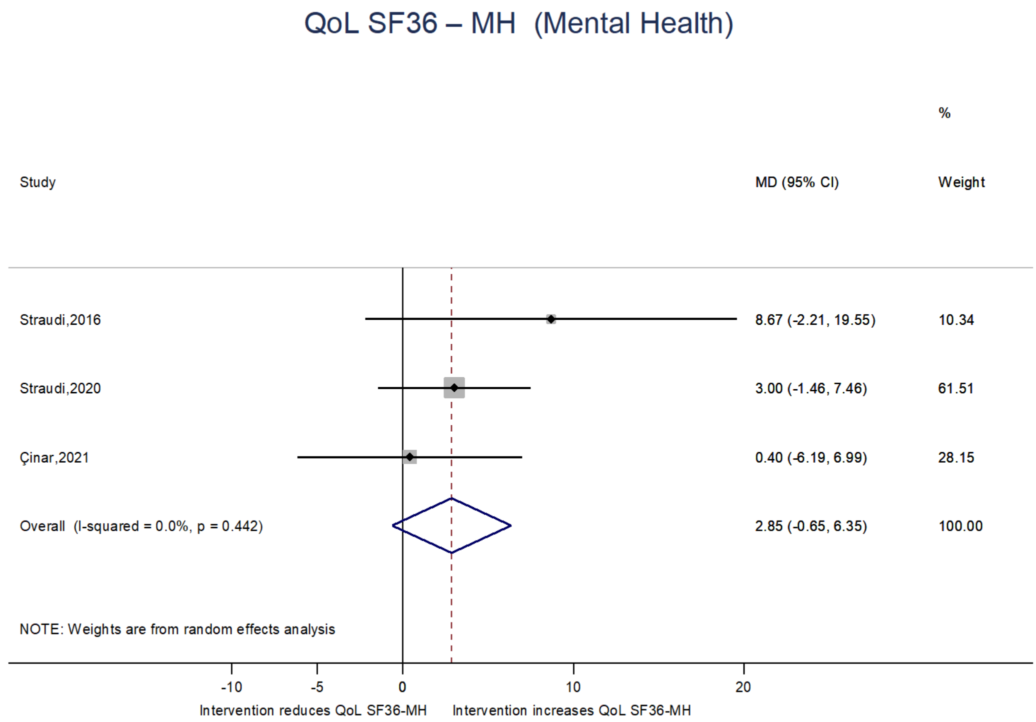

figure 7A: Pre-intervention QoL SF-36-MH

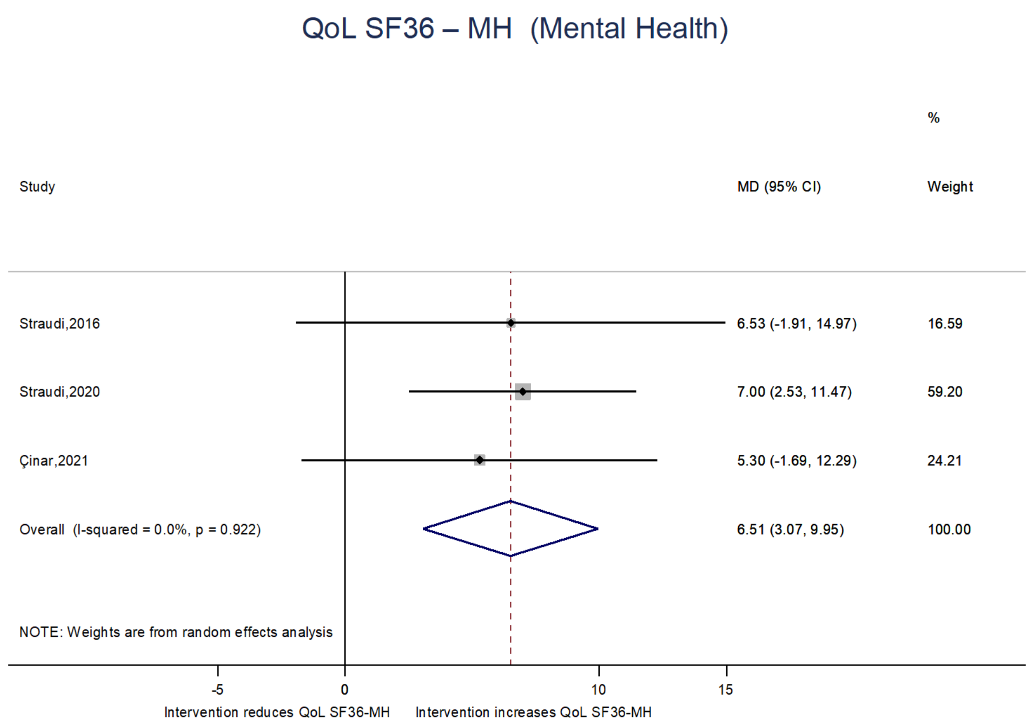

figure 7B: Post intervention QoL SF-36-MH

Risk of Bias

Thirteen studies described randomization method and allocation concealment[12–14,16,18–26]. Fourteen studies performed some type of blinding of participants and/or personnel[4,12–16,18,19,21–24,26,27], with one of them achieving double-blindness[22]. Ten studies described the reported outcomes of the RCT sufficiently in the study protocol[4,12,13,18,19,22–24,26,27] and all studies reported withdrawals, if any[4,12–28], with only one of them lacking in reporting the withdrawals' reasons[14].

Discussion

This review aimed at understanding the impact of robotic and exoskeleton gait training (REAGT) on patient's perspective of quality of life and well-being in general. 18 studies were approved as eligible for this review and 8 of them provided appropriate data for the conduction of a meta-analysis. From these 18 studies, 9, 8 and 1 enrolled MS, Stroke and SCI patients, respectively. Sixteen studies used Robotic Assistive Gait Training (RAGT) or Electromechanical Assistive Gait Training (EAGT) and two used exoskeletons for the gait training interventions. Sixteen different psychological assessment tools (or parts of tools) were used. From these 16 tools, MCS-36, QoL-36-SF, QoL-36-ER, QoL-36-GH, QoL-36-VT, QoL-36-MH and FSS were used in three studies or more and we proceeded to quantitative syntheses of the results. Meta-analysis of QoL-36-MH studies' results showed statistically significant superiority of the intervention compared to control groups. Additionally, meta-analysis of FSS results revealed a trend in improving patients' stamina or patient's fatigue perspective.

Either way, REAGT could be beneficial for patients' stamina, improving their cardiovascular or musculoskeletal system or/and putting an effort during REAGT seemed promising results. This is in agreement with previous research in athletes[53] concluding that physical and psychological components are communicating vessels. Similarly, all the eligible articles [14,16,21–25,28] showed improvements in physical aspects after REAGT gait training, although half of them[16,21,24,25] did not report statistically significant differences after intra-group comparisons.

Selecting an appropriate tool for recording psychosocial changes in patients with UMND seemed to be an area of diversity. Probably, researchers' main dilemma was either to use a generic tool for easier comparison with other studies or to use a disease specified tool (like Multiple Sclerosis Quality of Life-54 (MSQoL-54) or Stroke Specific Quality of Life Scale (SSQoL) for improved accuracy in the intervention effect.

Spinal Cord Injured Patients' and Stroke survivors' Quality of Life fluctuation has been described by previous researchers[54]. Depending to the severity of stroke, patients linger between decreasing their life expectations or alter their reality by multi-modal rehabilitation strategies, depending on their availability, cost and national health care systems. Long-term engagement to any rehabilitation program requires an increased level of psychological health securing this gap to the narrowest as possible. There are also concerns of an increased drop-out ratio in studies were patients had a depressed psychology after a sudden disability manifestation [55] and are assessed by disease specific, QoL (SSQoL) and psychological evaluation tools. And this is the need for the rehabilitation modalities and apparatus to have a proved positive psychological impact along with the physical one.

For the MS patients the existence of this gap is manifested wider to the younger patients[56]. Higher life expectations and the lack of a sense of coherence[57] put younger people in greater risk of psychological morbidity. Since MS is usually manifested to the age group between 20 and 40 years old, the psychological impacts of physical interventions and rehabilitation techniques obtain a great importance. Active commitment and engagement towards treating this illness[5] and therapeutic exercise[58] can play important roles to break or decelerate the vicious cycle of MS.

Resuming the above, SCI and Stroke with their sudden manifestation put patients in risk of psychological morbidity and low QoL[59,60] but even slowly progressive MS have similar results[61]. Coping strategies, given as guidelines, from articles and organisation web pages, always include physical activity and constant rehabilitation[62–64]. REAGT seems to include both psychological and physical morbidity coping strategies. With that in mind the results of our meta-analysis were not a surprise: all meta-analysed QoL subscales showed, at least, a beneficial trend after REAGT. We also came with a statistically important difference in QoL-MH (Mental Health) subscale, before and after the intervention. That might be the result of recruiting all mental and cognitive patients' abilities to adapt to the new rehabilitation modality and cooperate with the dedicated rehabilitation team.

Unfortunately, this work comes with some limitations: Despite our expectations, SCI studies were not represented equally to the total of the eligible studies. We assume that this phenomenon was due to the difficult stratification of SCI patients and probably a harder dilemma between the "Intention to Treat" and the "Per-Protocol" study concepts, especially when the study took place in one rehabilitation establishment. As for the quality of the studies, although most of them reached high standards, some failed to provide details of randomization and blinding. Comparison of RAGT+VR with RAGT-VR effects could be an area of future investigation, since VR immersion effect is crucial for patients with mobility limitations and could provide an alternative for patients that are not eligible for exoskeleton gait training or for rehabilitation centers were exoskeleton gait training is not provided. We expect to have more RCTs in this area at the future.

REAGT is a rehabilitation modality, constantly improving and adapting to the recent technologies as well as previous design and mechanical discrepancies. Combining with other rehabilitation techniques and a complete rehabilitation team, we advocate that REAGT is beneficial for QoL of SCI patients and especially for the mental health sector.

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