# Exercise effects on glucocorticoid induced bone loss in adults: a systematic review and meta-analysis

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**Short title:** Glucocorticoids and exercise effects on bone mineral density

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## Abstract

**Objectives:** Due to their pronounced anti-inflammatory and immunosuppressive effects Glucocorticoids (GC) are widely used in the field of inflammatory conditions and organ transplants. Unfortunately, GC-induced osteoporosis is one of the most common causes of secondary osteoporosis. The aim of the present systematic review and meta-analysis was to determine the effect of exercise added to GC-therapy on bone mineral density (BMD) at the lumbar spine or femoral neck in people under GC-therapy.

**Methods:** A systematic literature search of five electronic databases included controlled trials with a duration of more than 6 months and at least two study arms: (a) Glucocorticoids (GC), (b) GC and exercise (GC+EX) were conducted up to 20/09/2022. Studies involving other pharmaceutical therapies with relevant effects on bone metabolism were excluded. We applied the inverse heterogeneity model. Outcome measures were standardized mean differences (SMD) with 95%-confidence intervals (95%-CI) for BMD changes at the lumbar spine (LS) and femoral neck (FN).

**Results:** We identified three eligible trials with 62 participants in total. In summary, the GC+EX intervention indicates statistically significantly higher SMD for LS- (SMD: 1.50; 95%-CI: 0.23 to 2.77), albeit not for FN-BMD (0.64; 95%-CI: -0.89 to 2.17), compared with GC-treatment alone. We observed substantial heterogeneity (LS-BMD: $I^2$=71%, FN-BMD: $I^2$=78%) between the study results.

**Conclusion**: Although more well-designed exercise studies are needed to address the issue of exercise effects on glucocorticoid-induced osteoporosis (GIOP) in more detail, upcoming guidelines should already pay more attention to the aspect of exercise for bone strengthening in GIOP.

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**Key words:** glucocorticoid-induced osteoporosis, exercise, bone mineral density, adults

**Key message:**

- Exercise added to glucocorticoid therapy demonstrated significant effects on BMD at the lumbar spine.
- This finding should be verified by dedicated randomized controlled trials.

**Lay summary**

***What does this mean for patients?***

Based on our research, we suggest that patients with glucocorticoid induced osteoporosis should participate in regular exercise programs for osteoporosis and fracture reduction. This not only helps to prevent fall-related fractures but also to increase bone mineral density, particularly at the lumbar spine and proximal femur, which are skeletal sites very prone to fragility fractures. Nevertheless, more well-designed exercise trials are needed to address the issue of exercise effects on glucocorticoid-induced osteoporosis in more detail, and to look at different groups of people on glucocorticoid therapy.

# Introduction

Glucocorticoids with their anti-inflammatory and immunosuppressive effects are widely used for the treatment of acute and chronic inflammatory conditions or for preventing rejection after organ transplants [1]. About 2.7% of European postmenopausal women are currently taking glucocorticoids (cortisone/prednisone) [2]. However, glucocorticoid (GC)-induced osteoporosis (GIOP) is one of the most common causes of secondary osteoporosis [3]. GC-induced bone loss is most prominent in trabecular bone. A trabecular bone loss of 8% at the lumbar spine was reported for the initial 5 months of GC therapy; however, after discontinuation of the treatment, this bone loss seems to be (partially) reversible [4]. Nevertheless, vertebral fractures were observed in about 37% of women under long-term (i.e. ≥3 months) GC administration, with >14% of the patients having two or more asymptomatic vertebral fractures [5]. Considering the dose-dependent effect of GC on bone, the relative risks (RR) rise to a statistically significant RR 1.36 for non-vertebral, and RR 2.59 for vertebral fractures for doses of 2.5-7.5 mg/d prednisolone equivalent while doses of 7.5 mg/d and more double the adjusted relative risk for vertebral fractures (RR 5.18)([6, 7]). A number of antiresorptive and bone anabolic pharmaceutic agents (e.g. Alendronate / Risedronate / Zoledronate, Denosumab, Teriparatide) were recommended for the prevention [1] and therapy of GIOP [3, 8], in addition, the general recommendations for vitamin D and calcium supplements apply [3, 8, 9]. However, many people are looking for non-pharmaceutic options to prevent GC-induced bone loss. In general, dedicated physical exercise is a recognized agent for increasing bone strength [10] and preventing low-trauma fractures [11]. Nevertheless,

although physical exercise was recommended for preventing fall related fractures, none of the recent recommendations (e.g. [1, 3, 12] on prevention and treatment of GIOP refer to exercise as an agent for maintaining or increasing bone mineral density (BMD). Considering the few exercise trials with their limited statistical power to address this issue, this reticence is understandable. Thus, in order to determine the effect of exercise on bone during GIOP, the aim of the present systematic review and meta-analysis is to summarize the existing literature and to quantify the exercise effect on BMD at the lumbar spine and femoral neck in cohorts undergoing GC-therapy.

## Material and Methods

The literature search for the present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was registered in the International Prospective Register of Systematic Reviews [13](PROSPERO; ID: CRD42022308155).

Studies from five electronic databases PubMed/Medline, Scopus, Web of Science, Cochrane and CINAHL published up to 31 January 2022, with an update on 20 September 2022, were used for this review without language restrictions. A standard search protocol was developed using a standardized vocabulary.

Synonyms, truncations and subject headings (Mesh terms for Medline) were used to sensitize the following search query: ("osteoporosis" or “osteopenia" or “bone mass" or "bone turnover" or "bone mineral content" or "bone mineral density" or "BMD" or “BMC” or "bone density" or “bone loss" or “bone resorption” or “bone strength” or “demineralized bone” or “bone defect”) AND ("exercise" or "training" or "sports" or "physical activity" or “physical fitness” or “weight bearing” or “weight lifting”) AND ("glucocorticoids" or “corticosteroid” or “steroid” or "prednisolone" or “prednisone” or "cortison" or “corticosteron”).

The reference lists of the identified studies were reviewed and a manual search was performed in Google Scholar to identify additional relevant articles. To exclude duplicate publications, author names, title, abstract and date of publication were checked by the same reviewer (SK).

## Inclusion and exclusion criteria

Based on our research question: "In people with GOIP, what is the effect of exercise added to GC-therapy compared with isolated GC-therapy on BMD at the LS and hip use in controlled trials", we considered studies/study arms with the following inclusion criteria. (1) Studies with at least one exercise group versus a control group without additional physical training, both receiving the same glucocorticoid treatment. (2) Studies that determined areal BMD or bone mineral content (BMC) of the lumbar spine (LS) and/or femoral neck (FN) at baseline and end of the study as determined by (3) dual X-ray absorptiometry (DXA) or dual photon absorptiometry (DPA). (4) Studies with intervention duration ≥6 months. (5) Randomized and non-randomized controlled trials.

Human studies with (1) pharmaceutic agent others than glucocorticoids with relevant influence on bone metabolism, (2) cancer patients, (3) all kinds of intense physical activity or exercise prior to the exercise intervention, (4) participants exposed to weightlessness in space or permanent bed rest were excluded. Review articles, case reports, editorials, conference abstracts and letters were also excluded.

## Data extraction

Two reviewers (SK and WK) independently evaluated full-text articles and extracted data from all eligible publications. An extraction form was used to sample the relevant data of the publications, covering publication characteristics (e.g. author's name, year of publication, country), study details (e.g. study design, sample size, drop-out rate), participant characteristics (gender, health status, age, anthropometric data including baseline BMD-values; Tab. 1), pharmacologic therapy characteristics (Tab. 2), including details on glucocorticoid therapy, dietary supplements (calcium and vitamin D) and other medications, as well as exercise training characteristics (pre-intervention training status, monitoring/supervision of exercise, intervention duration, exercise protocol, type of exercise, intensity progression, attendance rate, activity in the non-exercise group) (Tab. 3).

## Study outcomes

The outcome measure was bone mineral density (BMD) at the lumbar spine and/or femoral neck (FN) determined by dual X-ray absorptiometry (DXA).

## Quality assessment

Eligible studies were assessed for risk of bias by two independent reviewers (SK and WK) using the Physiotherapy Evidence Database (PEDro) Scale Risk of Bias Tool [14] and the "Tool for the Assessment of Study Quality and reporting in Exercise" (TESTEX)[15] both specifically dedicated to physiotherapy/exercise studies. In case of inconsistencies, a third independent reviewer (SvS) made a decision.

## Data synthesis

Authors were contacted to provide missing data. When no reply was received or data were not available, confidence intervals (CI) or standard errors (SE) were converted to SD [16]. In detail only SE% had to be converted to absolute SD in the present study. One basically eligible study [17] that addresses our research questions within a subgroup analysis (GC+EX: n=3 vs. GC : n=12) was not considered due to a lack of data on absolute changes and variance of the changes (the authors were contacted, however data were no longer available). Due to the small number of studies, we did not perform subgroup analyses.

## Statistical Analysis

We conducted a meta-analysis using the metafor package [18] that is included in the statistical software R [19]. Effect size (ES) values were presented as standardized mean differences (SMDs) in combination with the 95% confidence interval (95%-CI). We applied the inverse heterogeneity (IVhet) model proposed by Doi et al. [20]. Heterogeneity between the studies was checked using $I^2$ statistics. $I^2$ of 0-40% was considered as "low", 30-60% as "moderate", 50-90% as "substantial" and 75-100% as "considerable" heterogeneity [21]. Assessment of small study/publication bias was conducted using funnel plots with trim and fill analyses applying the L0 estimator proposed by Duval et al. [22]. Funnel plot asymmetry was further checked using regression test and their standard errors using the t-test and Kendall's τ statistic for potential publication bias. Additionally, we used Doi plots and the Luis Furuya-Kanamori index (LFK index) [23] to check for asymmetry. LFK values within ±1 were considered negligible, while values ≥±1 to ±2 were considered as showing minor asymmetry. Values higher than ±2 indicate major asymmetry. P-value <0.05 was considered as the significance level for all the tests. SMD values of 0.2, 0.5, and 0.8 were considered as small, medium, and large effects [24].

**Please add "Fig. 1: Flow diagram of search process according to PRISMA [25]" about here**

# Results

## Study selection

Figure 1 illustrates the process of the study. After removing 283 duplicates, 1180 articles were screened based on title and abstract. The full texts of 11 potentially relevant articles were

screened and finally, a total of three articles [26-28] of two research groups were included in this systematic review and meta-analysis.

## Study- and participant characteristics

The three studies included in this systematic review and meta-analysis comprise three isolated Glucocorticoide groups (GC) and three combined Glucocorticoide and Exercise (GC+EX) groups (Tab. 1). All the studies were randomized controlled trials. The pooled number of participants was 62 (GC: 32, GC+EX: 30) and sample size in individual studies ranged from 8 to 16 participants per group (Tab. 1). One study each included only women [28] or men [26], another study [27] included both genders. Mean age of the cohorts ranged between 49±7 [27] and 56±11 [28]. Participants suffer from rheumatoid arthritis [28] or were lung [27]/heart transplant recipients [29] with the surgical procedure 2 months prior to the exercise intervention (Tab. 1). In contrast to the cohort with rheumatoid arthritis [28], baseline BMD at the LS was low [26] or very low [27] respectively in the studies that included heart [26] or lung transplant [27] recipients. Moreover, in the latter cohorts a statically significant BMD-loss of 12-15% at the LS (5-6% for FN-BMD [29]) occurred during the two months between the transplantation and the start of the intervention.

**Please add "Tab. 1: Baseline characteristics of the studies" about here**

## Glucocorticoid treatment characteristics.

Table 2 gives the characteristics of the glucocorticoid therapy. In summary, in all studies prednisone / methyl-prednisolone was administered, albeit in different modes and diverging doses. In the two studies with the lung or heart transplant recipients, GC-therapy started with high doses during and immediately after surgery and then successively reduced GC to doses to about 10 mg/d after 5-6 months [26, 27]. Westby et al. [28] which included rheumatoid arthritis patients, on the other hand, scheduled a lower and continuous GC-administration of 2.5-7.5 mg/d. Due to the well-documented GC-therapy-induced reductions in calcium absorption in both the gut and the renal tubule of importance [30], only Westby et al [28] supplemented calcium (1000 mg/d) and Vit-D (400 IU/d), while baseline data or data on Ca substation were not reported by Braith et al. [26] or Mitchell et al. [27].

**Please add "Tab. 2: Medication characteristics" about here**

## Exercise characteristics

Characteristics of the exercise protocols of the included studies are displayed in Tab. 3. Briefly, all the studies included untrained participants. Apart from the intervention of Westby et al [28] that applied a mixed moderate intensity aerobic dance and low intensity dynamic resistance exercise training, the two other studies [26, 27] focus on isolated dynamic resistance exercise training (DRT) exercises on machines with special emphasis on lumbar extension exercise to muscle failure/repetition maximum. Braith et al. [26] and Westby et al.

[26, 27] scheduled 3 sessions per week, while Mitchell et al. [27] scheduled one session with a single set of 15-20 reps (7 s/rep) to muscle fatigue on the MedX lumbar extension device. With six [26, 27] and 12 months [28] the interventions of the studies can be considered short to moderately long. Although of short duration, Braith et al. and Mitchell et al. [26, 27] considered progression of exercise intensity in their protocols.

**Please add "Tab. 3: Exercise characteristics" about here**

## Study outcomes

All three studies determine BMD of the LS, two of them [26, 28] additionally address BMD at the FN, consistently via DXA technique.

## Methodologic quality

Following the suggestion of Ribeiro de Avila et al [31] the methodologic quality of the studies according to PEDro [14] can be considered low (<5 score points) to moderate (5-6 score points) (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). In particular, aspects related to blinding/allocation concealment were not satisfied or not reported. With respect to TESTEX [15], the studies range from 7-9 of available 15 score points. Of note, no study reported information concerning adverse effects of the intervention or activity monitoring in the control groups (Supplementary Table S1).

## Study outcomes

BMD of the LS was maintained [28] or decreased (statistically non-significant: [26], statistically significant: [27]) in the combined GC+EX group while LS-BMD decreased (statistically significant: [26, 27]) in all the isolated GC group. Apart from the study of Westby et al. [28] differences between GC+EX and GC were statistically significant [26, 27]. In parallel the two studies [26, 28] that address FN-BMD reported statistically non-significant reductions in their exercise and GC groups. While Braith et al. [26] reported statistically significant higher reductions in their isolated GC-groups, no relevant FN-BMD differences between GC+EX and GC were observed by Westby et al. [28].

# Meta-Analyses Results

Three comparisons addressed exercise effects at BMD-LS (Fig. 2a). In summary, the inverse heterogeneity model (IVhet) (Fig. 2a) with imputation of the mean correlation demonstrated a statistically significant effect (p<.021) of exercise on GC+EX vs. GC at the LS (SMD: 1.50; 95%-CI: 0.23 to 2.77). Heterogeneity between the trial results ($I^2$=71%) can be classified as substantial (Fig. 2a).

**Please add "Fig. 2: Forest plot of meta-analysis results for lumbar spine (A) and femoral neck BMD (B)" about here.**

Figure 2b displays results for the additionally effect of exercise on GC therapy vs. isolated GC therapy on BMD at the FN. Based on only two eligible studies, we observed no statistically significant positive effect (p=.412) of the combined therapy (SMD: 0.64; 95%-CI: -0.89 to 2.17). Heterogeneity between the trial results was substantial (78%) (Fig. 2b).

### Publication/small study bias

The funnel plot analysis with trim and fill suggests considerable evidence for a publication/small study bias for the LS-BMD analysis (Fig. 3). The analysis imputes two missing studies on the lower right-hand side (i.e., small studies with negative outcome). The corresponding asymmetry was confirmed when inspecting the LFK Index (1.1 = minor asymmetry). Additionally, the regression (p=0.026), but not the rank correlation test (p=.333) for funnel plot asymmetry, observed statistically significant funnel plot asymmetry.

**Please add "Fig. 3 Funnel plot with trim and fill on the effect of exercise on BMD at the lumbar spine" about here.**

Funnel plot analysis (not shown) and other diagnostic tests do not indicate evidence for a publication/small study bias for the FN-BMD. However, due to the low number of studies included in the analysis (n=2), the tests predominately failed to generate reliable data.

## Discussion

Reviewing current guidelines on GIOP (e.g. [1, 3, 12], exercise is considered in the area of fall prevention, if at all. However, the potentially more important aspect of GOIP is the pronounced bone loss in particular during the first year of treatment [32]. Thus, the aim of the present systematic review and meta-analysis was to provide evidence for the effect of exercise on BMD at the lumbar spine and proximal femur in people with ongoing GC-therapy. After a comprehensive search process, unfortunately only three studies were eligible to be included in the analysis. One may argue that this low number might prevent a meaningful meta-analysis on the effect of exercise on GC-effects in people with GIOP. However due to the fact that the trials included featured comparable study designs (RCT), participant age, sample size and that two [27, 29] of the three studies were very similar, we opted to conduct a joint (meta-)analysis, albeit applying the robust inverse heterogeneity (IVHet) model (see below).

In summary, we observed a statistically significant positive effect of exercise on BMD at the lumbar spine, however not at the FN. We mainly attribute this result to the higher amount of trabecular bone at the LS predominantly affected by GIOP [4, 7]. The two studies that determined BMD at the LS and FN [26, 28] did in fact report considerably higher bone loss at the LS (Fig. 2) compared to the FN-ROI (Fig. 3), enabling a higher potential of positive effects for LS-BMD. Thus, one may argue that differences in baseline BMD (Tab. 1) contribute to the study outcomes. However, there is only limited evidence [33] that cohorts with (very) low

baseline BMD (i.e. [27, 29]) benefit that much more from exercise compared with cohorts with normal BMD. Also of note, those two studies with high-dosed GC-therapy (Tab. 2) administered after heart [29] or lung transplants [27] were the ones which revealed significant positive BMD effects. Both exercise studies were only 6 months of duration and thus might have predominately addressed the pronounced bone resorption observed during the first 5–7 months of GC-treatment [32]. Of surprise however, in two studies [27, 29] the exercise intervention did not only slow down GC-induced bone loss but restored LS-and FN BMD close to pre-GC-therapy levels. There is some evidence that the tapering of GC doses during the intervention contributed to this result (Tab. 2). Indeed, the GC-group of the study of Braith et al. [29] revealed a maintenance of BMD at LS and FN after 3 months of intervention. Reviewing the exercise protocols of both studies on transplant recipients [27, 29], a common component was back-strengthening exercise on a dedicated lumbar extension resistance device once per week. Of note, Mitchell et al. [27] prescribed only sets of 15-20 repetitions to voluntary muscle fatigue with particular emphasis on the eccentric component (2s concentric–1s isometric-4s eccentric) of the movement - a time-effective exercise protocol feasible even for people with low enthusiasm for exercise. However, the sedentary and physically limited status of the heart and lung transplant recipients might have contributed to the significant exercise effects on LS-BMD and FN-BMD. Thus, it is debatable whether this finding can be transferred to cohorts with higher baseline fitness levels and higher baseline BMD i.e. cohorts with rheumatoid arthritis.

The study that addressed rheumatoid arthritis with low dose prednisone (2.5 to 7.5 mg/d) [28], i.e. a much more common scenario for GC-treatment compared to the immunosuppressive approach discussed above, displays non-significant results for BMD-LS (p=.09) and –femoral neck (n.g.). In contrast to the studies with transplant recipients that applied dedicated back-strengthening programs on resistance machines specifically constructed for this purpose, the exercise protocol of Westby et al. [28] focused on aerobic dance without high impact components and low-intensity DRT for “major peripheral muscles”. It is likely that this non-(site)-specific low intensity exercise protocol and the low sample size of the study (n=10/group) included in the final BMD analysis might have prevented statistically significant results.

Of further importance, two [26, 27] of the three studies applied exercise protocols of 6 months, usually too short for determining the full amount of mineralized bone during a remodeling cycle [34, 35]. However, considering the mode of action of GIOP with rapid and pronounced bone loss during the first 5-7 months of GC supplementation [32], an exercise-induced reduction of GC-triggered bone loss might explain the corresponding “short-term” effects.

Our positive meta-analysis result on exercise-induced effects on BMD at least at the LS could not necessarily be expected. As discussed, chronic administration of GCs can have significant catabolic effects on muscle [36, 37] and bone [37, 38]. Apart from dedicated effects on bone cells [1, 39], systemic effects of GC-therapy might prevent positive effects of exercise/mechanical loading on bone. This refers to calcium malabsorption in the gut/renal tubule [30], hyperparathyroidism [40], and in particular the suppression of the somato- and gonadotropic axis [1, 41]. It is also possible that the resorptive potency of sclerostin and RANK, which show an elevated expression by glucocorticoids, are counteracted at the cellular level.

Apart from the very limited number of eligible studies and their low sample sizes, other limitation and study particularities should be considered to properly interpret our results. (1) Two of the three studies [26, 27] focus on the immunosuppressive effects of GC therapy. Both trials started GC-therapy immediately during/after heart and lung transplant and correspondingly administered (very) high initial GC-doses (Tab. 2) that were successively reduced to about 10 mg/d by study end (8 months). In contrast, Westby et al. [28] applied a continuous dose of 2.5-7.5 mg/d in the rheumatoid arthritis cohort for 12 months. Although no corresponding information was provided for the latter study, it is likely that GC-therapy was initiated years before study start, i.e. the initial phase of rapid OC-induced bone loss was already terminated [1, 32]. This feature might have reduced the effect of exercise to positively address BMD in this cohort. (2) Baseline BMD varied between the exercise trials with low [29] to very low [27] LS-BMD values in the transplant cohorts and normal BMD in the rheumatoid arthritis group [28]. There is some evidence that low baseline BMD might be related to higher exercise-induced BMD increases [33], which would be in line with the results of the present analysis. (3) Unfortunately, two of three studies (Tab. 1 and 2) did not report drop-out or exercise attendance rate, aspects that indicate the feasibility and acceptance of the training protocol. However, bearing in mind the high level of suffering and limitation due to heart or lung transplants, we assume that the aspect of the attractiveness of the exercise training program is negligible in this context. (4) We applied the inverse heterogeneity model (IVhet) [20] that is less susceptible to underestimation of statistical error in heterogeneous studies; i.e., the results are more reliable in heterogeneous studies especially with respect to the coverage probability of confidence intervals [42].

## Conclusion

In summary, the present systematic review and meta-analysis provided evidence for a positive effect of exercise on bone health during GC-therapy. Our meta-analysis is based on only three randomized controlled trials. Further, the two studies that reported statistically significant results focus on immunosuppressive therapy after heart or lung transplants, which is a less common scenario for GC-treatment. Thus, generalization of our results to other cohorts with GIOP is limited and the present finding should be carefully interpreted. As a

consequence, further, well-designed exercise trials will have to focus on the effect of exercise on bone mineral density in GIOP to provide a definite conclusion on this issue. Nevertheless, considering the time effectiveness of present exercise protocols on BMD, we feel that upcoming recommendations and guidelines on GIOP should include exercise more prominent as a tool for bone strengthening.

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## Author Contributions

SK and WK initiated the present meta-analysis. The literature search was carried out by SK and WK. Data analysis and interpretation, was conducted by SK, SvS, MK, UL and WK. All the authors contributed to quality assessment and drafted and revised the manuscript. SK and WK accepts responsibility for the integrity of the data sampling, analysis and interpretation.

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## Disclosure statement

The authors have declared no conflicts of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author (WK) upon reasonable request.

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## Figure legend

**Fig. 1:** Flow diagram according to PRISMA [25].

**Fig. 2:** Forest plot of meta-analysis results for lumbar spine (A) and femoral neck BMD (B).

**Fig. 3:** Funnel plot with trim and fill on the effect of exercise on bone mineral density at the lumbar spine.

# Tables

**Tab. 1: Baseline characteristics of the studies/participants**

| Author, year | Study arm | Number of participant (gender) [n] | Health status | Age [years] | Body- height [cm] | Body-mass [kg] | BMD-LS baseline [g/cm³] | BMD-FN baseline [g/cm³] | Drop-out [%] |
|---|---|---|---|---|---|---|---|---|---|
| **Braith et al. 1996** | Glucocorticoids | 8 (m) | Heart transplant recipients | 56±6 | 173±9 | 85±11 | .716±.087 | .921±.078 | n.g. |
| | Glucocorticoids + Exercise | 8 (m) | | 56±6 | 173±5 | 78±8 | .701±.064 | .972±.085 | |
| **Mitchell et al. 2003** | Glucocorticoids | 8 (w: 1, m: 7 | Lung transplant recipients | 55±6 | 173±13 | 81±20 | .528±.180 | ----- | n.g. |
| | Glucocorticoids + Exercise | 8 (w: 2, m: 6) | | 49±7 | 173±10 | 72±19 | .543±.170 | ----- | |
| **Westby et al. 2000** | Glucocorticoids | 16 (w) | Rheumatoid Arthritis | 56±11 | 164±7 | 63.4±13.6 | 1.004±.141 | .755±.055 | 7 |
| | Glucocorticoids + Exercise | 14 (w) | | 56±10 | 162±8 | 61.7±10.8 | .969±.118 | .726±.118 | |

m: men, w: women

**Tab. 2: Medication characteristics of the studies**

| Author, year | Glucocorticoid | Start of pharmaceutic therapy | Calcium | Vitamin D | Other medication |
|---|---|---|---|---|---|
| **Braith et al. 1996** | Progressive reduction from 1000 mg/d to 10 mg/d oral methyl-prednisolone after 20 weeks, in case of acute rejection (n=20) higher doses | During surgery, i.e. two months pre-exercise | n.g. | n.g. | n.g. |
| **Mitchell et al. 2003** | Progressive reduction from 500 mg/d (surgery) to 10-15 mg/d oral methylprednisolone during the intervention | During surgery, i.e. two months pre-exercise | n.g. | n.g. | Cyclosporin, azathioprine, details n.g. |
| **Westby et al. 2000** | Continuously 2.5 to 7.5 mg/d prednisone | n.g. (..taking continuous low-dose prednisone) | Calcium-carbonate 1000 mg/d | 400 IU/d | DMARDs; non-steroidal anti-inflammatory drugs (NSAID) details n.g. |

n.g.: not given

**Tab. 3: Exercise characteristics of the studies**

| Autor, year | Pre-intervention exercise status | Design/ Supervision | Intervention-length (months) | Type of exercise | Exercise protocol | Progression of intensity | Attandance | Activity in control group |
|---|---|---|---|---|---|---|---|---|
| **Braith et al. 1996** | n.g. presumably (DRT) untrained | RCT consistently supervised | 6 | DRT, all main muscle groups at machines | 3 sessions per week: 1x week lumbar extension at specific MedX device and 2x week 8 upper and lower body exercises with 1 set of 10-15 reps at RM, walking training with similar intensity and volume (n.g.) in both groups | yes | n.g | walking |
| **Mitchell et al. 2003** | untrained | RCT, consistently supervised | 6 | DRT lumbar extension training on machine | 1 session per week lumbar extension at specific MedX device; 1 set with 15-20 reps to voluntary muscle fatigue, time under tension/rep: 2 s (concentric) – 1 s isometric – 4s eccentric) walking training with similar intensity and volume (n.g.) in both groups | yes | n.g. | walking |
| **Westby et al. 2000** | untrained | RCT, predominat-ely non-supervised | 12 | Aerobic Dance and DRT (major peripheral muscle groups) | 3x week, 15-20 min of moderate intensity aerobic dance, 10-15 min of floor exercises, cuff weight exercises with low intensity; more details n.g. | n.g. | 71% | n.g. |

DRT: Dynamic Resistance Training; n.g.: not given; RCT: randomized controlled trial; reps: repetitions; RM: repetition maximum (i.e. work to failure)

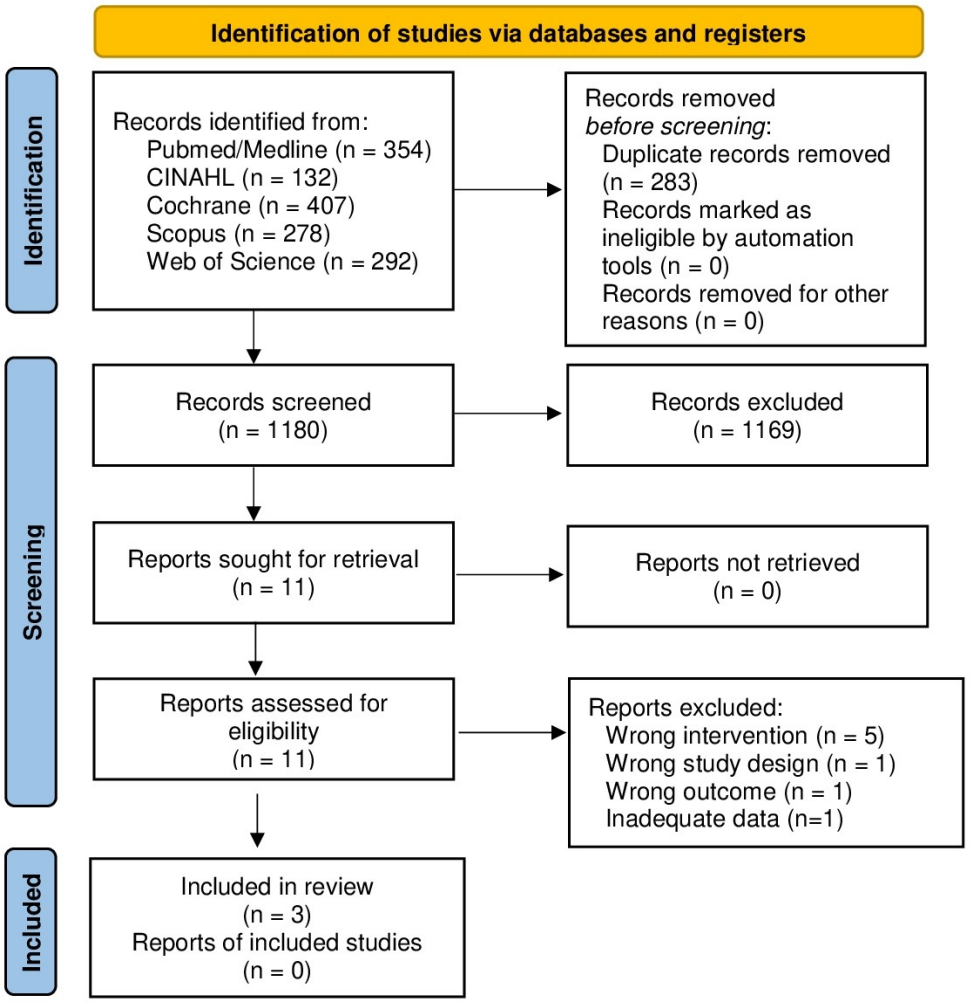


Fig. 1: Flow diagram according to PRISMA [25]

303x306mm (96 x 96 DPI)

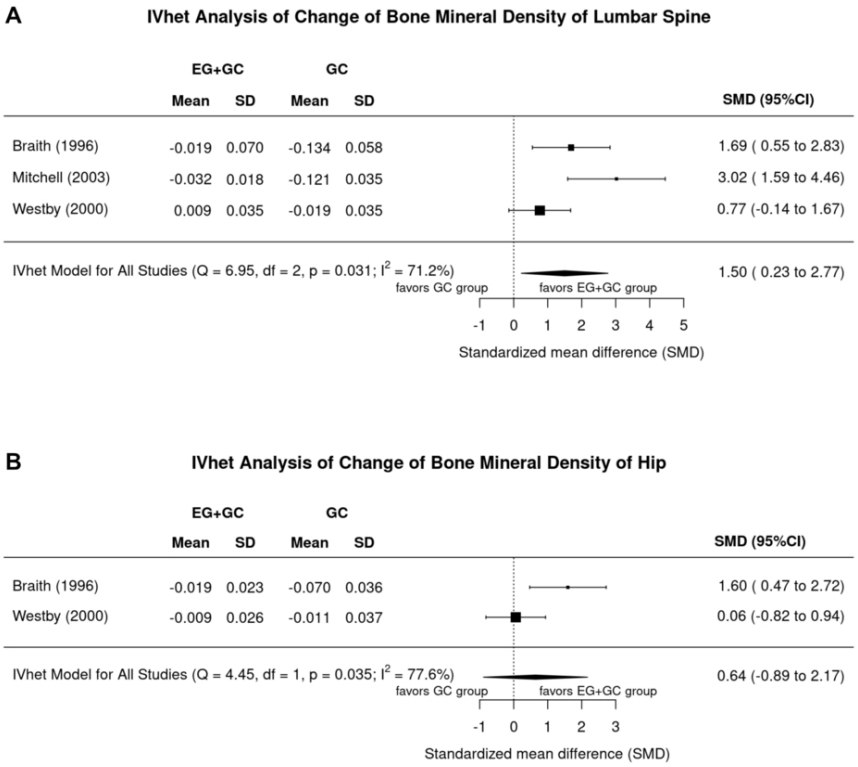


Fig. 2: Forest plot of meta-analysis results for lumbar spine (A) and femoral neck BMD (B).

91x78mm (300 x 300 DPI)

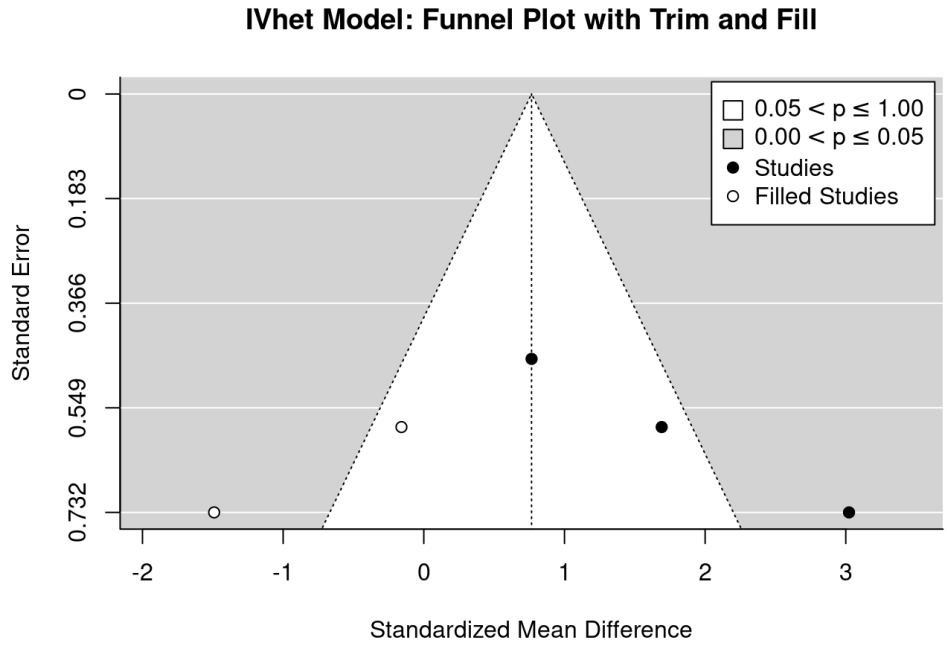


Fig. 3: Funnel plot with trim and fill on the effect of exercise on BMD at the lumbar spine.

449x320mm (76 x 76 DPI)