Impact of high-load resistance training on bone mineral density in osteoporosis and osteopenia: a meta-analysis

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Keywords: osteoporosis, exercise, resistance training, bone mineral density, meta-analysis

Abstract

Introduction

Osteoporosis is defined as a bone disorder that increases the risk of fracture due to decreased bone strength [1]. Osteoporosis leads to fragility fractures, thereby decreasing the quality of life and increasing the mortality rates and overall economic costs [2]. A study reported that the numbers of both men and women at high risk of osteoporosis fractures in 2010 are expected to double by 2040 [3], which emphasizes that this condition needs urgent attention.

Increasing bone mineral density (BMD) is key in preventing and treating osteoporosis, and exercise intervention involving load is recommended as a non-pharmacotherapeutic approach to increase BMD [4]. It has been shown that typical load exercises, such as resistance training, are effective in increasing BMD [5], and effective strategies have been studied from various perspectives, such as types, frequency, and combination of training [6, 7].

Load quantity is an important factor in resistance training, and there are reports linking the load quantity in resistance training to the resulting BMD. In a meta-analysis of 14 randomized controlled trials (RCTs) to investigate the effect of high-load resistance training (HLRT) on the BMD in post-menopausal women, HLRT led to a

significant increase in BMD in the lumbar spine, but not in the femoral neck [8]. It has been suggested that HLRT is more beneficial than normal resistance training in improving lower limb strength [9], and it is the most effective approach in strengthening muscles, regardless of the age [10, 11]. Reports in recent years have revealed that a decline in muscle strength is directly involved in bone fracture risks [12], and HLRT, which can improve both muscle strength and BMD simultaneously, may become an effective intervention to prevent fragility fractures.

Meta-analyses that examined HLRT and its effect on BMD have been limited to post-menopausal women and did not strictly concern osteopenia patients. The prevalence of osteoporosis is not low in men [13], which indicates that studies need to be performed on all patients with osteopenia, including males. In recent years, there has been an increase in the number of studies on osteoporosis patients [14, 15] and men [16, 17]. Although these studies reported that HLRT improved BMD, due to some differences in indicators used to evaluate BMD and small sample sizes obscuring the improvement in BMD being seen relative to the control group, there is yet to find a consensus on the relationship between HLRT and BMD.

Therefore, we aimed to verify the effect of HLRT on BMD in patients with osteoporosis using systematic review and meta-analysis approaches.

Materials and Methods

Database searching

We conducted a systematic review according to the procedures recommended in the PRISMA Statement [18]. A comprehensive literature search was performed using the electronic databases of PubMed, MEDLINE, CINAHL, Web of Science, Cochrane Reviews, and Cochrane Central Register of Controlled Trials. For each database, the search range was set from the time of its installation to June 2020. A manual search was performed using the citation list of papers as needed.

The database key words used were “osteoporosis,” “osteopenia,” “menopause,” “high intensity,” “loading,” “exercise,” “resistance,” “strength,” “heavy weight,” “training,” and “weightlifting,” and we combined these in order to execute the search (details have been described in the Online Resource). This study was registered in the International Prospective Register of Systematic Reviews (Registration number, CRD42020188034).

Study eligibility

The eligibility of a paper was determined in the following manner. Subjects had to be community-dwelling patients diagnosed with primary osteoporosis or osteopenia (diagnostic criteria: osteopenia, T-score < -1.0; osteoporosis, T-score < -2.5) [19], for whom the intervention was HLRT. The definition of HLRT included multi-joint exercises needed to improve muscle strength, and a single menu of exercises had to include 1–3 sets of 8–12 repetitions of a load with more than 60–70% of one repetition maximum (RM) [11, 20]. The intervention period had to be three or more months for the effect of resistance training on bone metabolism to become evident [21]. We did not specify the presence or details of the intervention in the control group. The outcome was set as the BMD of the femur and lumbar spine, which accurately reflects the bone fracture risk [22]. We only examined RCTs. Manuscripts and meeting minutes in languages other than English were excluded from the analysis.

Data extraction

The papers were chosen by two authors according to the eligibility criteria. Each author checked and screened the abstract and main text of each paper, and the opinion of a third person was considered for papers that the two authors disagreed on. We decided whether to use the papers after discussions.

If a study consisted of three groups, we chose the comparisons most relevant to our research question to avoid participants from the same group participating twice. The papers adopted were described in terms of their authors, basic information of the subjects, what was done for the intervention and the control group, intervention period, measurement device and area of interest, frequency of exercise, and adverse events.

Risk of bias assessment

Two authors independently evaluated the bias risk for each study. Bias risk was evaluated according to the Revised Cochrane risk of bias tool for randomized trials (RoB 2) [23]. Five items were evaluated: (1) bias arising from the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in the measurement of the outcome, and (5) bias in the selection of the reported result. Each item was evaluated as low risk, some concerns, or high risk. The final result of the overall risk-of-bias judgment was determined through discussions among the authors.

Meta-analysis

Meta-analysis was performed using Review Manager (version 5.4), and forest plots were created. The primary outcome was the BMD of the lumbar spine, total hip, or femoral neck, and the post-intervention mean differences and standard deviations for the HLRT and control groups were extracted from the data summary presented in each study. If a paper did not mention BMD results before and after the intervention and standard deviations, we contacted the authors of the paper by e-mail. When there was no description of the mean difference in the manuscript of a paper, we calculated it based on the information presented in the manuscript. Furthermore, where there was only mention of the 95% confidence interval (CI) and no description of the standard deviation, we used a conversion formula to calculate the standard deviation. If a paper lacked a standard deviation of the mean difference, we calculated it according to the procedures in the Cochrane handbook [24]. Harding et al. [17] reported the changes and standard deviation of changes. We calculated the correlation coefficient from this study (r=0.99), and we calculated the standard deviation of changes in the intervention and control groups using the pre-intervention and post-intervention standard deviations. Taking into consideration that the changes in BMD were represented in different units, such as the actual value or percentages, and that there were differences in the devices used to evaluate BMD, the data used for analysis were the standardized mean difference (SMD) of the BMD before and after the intervention. The data were converted to SMD using the calculation tools on the Review Manager. The calculation formula is installed on Statistical Algorithms in Review Manager 5.1 [25]. The effect was estimated using the random-effects model, and all results were shown in terms of SMD and 95% CI.

The presence or absence of heterogeneity between studies was evaluated by the χ^2 test, using Cochran's Q-test. In addition, the extent of heterogeneity was evaluated using I^2. An I^2 value of 0–40% generally indicates an insignificant level of heterogeneity; 30–60% indicates "moderate heterogeneity"; 50–90% indicates "substantial heterogeneity”; and 75–100% indicates “considerable heterogeneity” [25].

Furthermore, subgroup analysis was conducted to examine the consistency of the results. Subgroup analysis was performed on the following parameters: mean age of the intervention group (60 years or older: elderly, 60 years or younger: middle age), sex, total sessions (grouped according to the median of the selected articles; 64 or more sessions: high, 63 or fewer sessions: low), excluded high risk of bias, and the presence or absence of exercise intervention in the control group. In addition, meta-regression analysis was conducted to examine the effect of age, sex, total sessions, presence of high risk of bias, and presence of exercise intervention in the control group on the results, which were used as criteria for the subgroups. Meta-regression analysis was performed using EZR [26]. In all analyses, the significance level was set at 5%.

Publication bias was evaluated visually from the funnel plot. Visual assessment of a funnel plot is regarded as a common method for evaluating publication bias during meta-analysis [27]. The funnel plots were created using EZR [26].

Results

Fig. 1 shows a flow chart of the literature search. By screening the titles and abstracts of the articles in the search results obtained from each database, we selected 106 articles that fulfilled the eligibility criteria for this study. In addition, by screening the full text, we excluded a total of 97 articles because the subjects did not have primary osteoporosis or osteopenia (n=59), the subjects overlapped (n=7), the method of intervention was not HLRT (n=14), there was no control group (n=2), BMD was not a studied outcome (n=13), or the study was not randomized (n=2). Finally, nine RCTs were included in this study [14–17, 28–32].

Table 1 summarizes the papers used for analysis. A total of 259 subjects (116 men and 143 women) were included in the intervention group and 236 subjects (88 men and 148 women) in the control group. The mean age of subjects ranged from 42.1 to 83.0 years. The intervention period ranged from 12 to 54 weeks. In six studies, exercise interventions such as mild load resistance training, jump training, or agility training were included for the control groups. In all studies, dual-energy X-ray absorptiometry (DXA) was used to measure BMD. One of the studies had used quantitative computed tomography along with DXA for the measurements. BMD measurements of the lumbar spine, femoral neck, and total hip were obtained in eight, seven, and seven studies, respectively.

Table 2 shows the evaluation of bias in the selected papers. Three papers were evaluated as low risk, three papers as having some concerns, and three papers as at high risk of bias. The factors that we considered to increase the risk of bias were the unknown impact of dropouts and the uncertainty in outcome reporting. In addition, there were many cases of dropouts in the high-risk papers, and we hypothesized that these dropouts would have a large impact on the results.

Fig. 2 shows the results of the meta-analysis on HLRT and lumbar spine BMD. The HLRT group had a greater increase in lumbar spine BMD than the control group (SMD=1.40, 95% CI=0.68–2.12, $p<0.001$). There was also a very high degree of heterogeneity (Q=67.16, $p<0.001$, $I^2=90\%$).

Fig. 3 shows the results of the meta-analysis of HLRT and femur BMD. The HLRT group had a greater increase in both the femoral neck BMD (SMD=0.86, 95% CI=0.05–1.67, $p=0.04$) and total hip BMD (SMD=1.26, 95% CI=0.45–2.08, $p=0.002$) than the control group. Both the femoral neck (Q=75.53, $p<0.001$, $I^2=92\%$) and the total hip (Q=68.49, $p<0.001$, $I^2=91\%$) showed a high degree of heterogeneity in the results.

Fig. 4 shows the funnel plot. There was a horizontal asymmetry in the lumbar spine, femoral neck, and total hip by visual assessment.

Table 3 shows the results of the subgroup and meta-regression analyses. For the lumbar spine, the HLRT group showed a significant increase in BMD in all the subgroups analyzed except for the only men group. The total sessions low group showed no heterogeneity in the subgroup analysis in the lumbar spine. The other analyses showed significant heterogeneity (I^2=70–94%).

In the femoral neck, only the total sessions high group showed a statistically significant increase in BMD. Subgroup analyses except for the total sessions low group showed statistically significant heterogeneity (I^2=86–98%).

In the total hip, only men group, elderly group, total sessions high group, and control group with no exercise showed a significant effect of increasing BMD. Heterogeneity was observed in all subgroups except for only men group (I^2=68–96%).

The results of the meta-regression analysis showed that none of the factors were significantly associated with the lumbar spine. For the femoral neck, both the total sessions high and low groups showed significant associations (both $p<0.001$); for the total hip, excluded high risk of bias ($p=0.003$) and total sessions high and low groups ($p=0.005$) showed significant associations.

Discussion

As a result of the systematic search focusing on HLRT, osteoporosis, and osteopenia, we were able to extract nine RCTs involving 495 subjects. The results of the overall analysis suggested that HLRT is effective for maintaining and improving the BMD of the lumbar spine and femur in patients with osteoporosis and osteopenia.

HLRT takes advantage of the property of bones to change in amount and strength according to the magnitude of the strain [33, 34] in order to increase BMD through the strain caused by high-resistance training. The results of this study showed that the increase in BMD by HLRT also applies to actual osteopenia patients. Furthermore, resistance training promotes the secretion of humoral factors, such as testosterone, growth hormones, insulin-like growth factor-1, and myokine interleukin-6 [35, 36]. It has been shown that these humoral factors are related to bone metabolism [37], and the activity of humoral factors brought about by muscle activity may explain the increase in BMD resulting from HLRT that involves intense muscle activity.

The results of this study showed a high degree of heterogeneity regardless of the site of BMD measurement, and caution should be exercised while interpreting the results. For BMD of the lumbar spine, no statistically significant factors were extracted by meta-regression analysis. Only the subgroup analysis of the lumbar spine in the only women group showed a statistically significant BMD-increasing effect of HLRT and the lowest heterogeneity. Analysis of the total hip in the only male group showed a significant BMD-increasing effect and the absence of statistical heterogeneity. Although the specific mechanism is unknown, a study of healthy elderly people who underwent HLRT reported that despite not reaching the statistical significance, the male group tended to have a greater increase in lumbar spine bone density than the female group [38], and the variation in effect size may be influenced by gender differences.

As a factor of heterogeneity in our meta-analysis, the meta-regression analysis showed that the statistically significant associations were observed for the total sessions multiplied by the frequency and duration of interventions in the femoral neck and total hip analysis. In postmenopausal women, a proportional relationship between the amount of weight lifted and the increase in BMD over 1 year was found independently of factors such as age, body size, and the presence of hormone therapy [39]. Therefore, it is possible that the effect of HLRT on BMD is not only due to load quantity, but also due to the effect of total sessions related to the amount of weight lifted, which may have caused variation in the effect size and increase in the heterogeneity. In addition, the amount of weight lifted in the lumbar spine group was higher due to the addition of HLRT for the upper extremities and trunk, suggesting that total sessions had less effect on the heterogeneity of results than that in the lower extremity joints. The high risk of bias was also statistically significantly associated with heterogeneity in the total hip results. Papers with a high risk of bias had results with point estimates of effect sizes and CIs that were in the extremely positive direction, which may have resulted in high heterogeneity due to the overestimation of the effects of HLRT. Considering the lack of robustness in the subgroup analyses of both femoral neck and total hip, and the lack of trend in the effects of exercise interventions on femoral BMD in meta-analyses examining the effects of exercise intervention in postmenopausal women [5-8], it is difficult to clearly state the effect of HLRT on increasing femoral BMD in this study.

In terms of safety, although there were some mild adverse events, such as muscle pain, similar to previous meta-analyses on resistance training in post-menopausal women [6–8], no serious adverse events, such as bone fractures, were found in this study. A study that tested the safety of HLRT in women with low BMD reported that there were no adverse events, and subject compliance with the exercise intervention was favorable [40]. Furthermore, no adverse events were reported in the study that examined the performance of HLRT on patients who had suffered proximal femoral fractures [41]. HLRT is regarded as safe even compared to high impact jumping that involves a lot of joint load. However, many papers analyzed in our study involved guidance from a specialist provided with the intervention which suggests that the intervention from a specialist would be needed for clinically safe and effective implementation of HLRT. Since all papers in this study that simultaneously evaluated BMD and the effect of the intervention on muscle strength [14, 16, 17, 31, 32] showed improvements in muscle strength and motor function, HLRT may become a useful non-pharmacotherapeutic intervention for preventing fractures in osteopenia patients with reduced muscle strength as long as safety can be ensured.

This study has several limitations. First, although we selected papers in which subjects were clearly determined to have osteoporosis or osteopenia, we may have excluded papers on patients exhibiting clinical signs of osteoporosis, and there may be a selection bias involved in the study. Second, the high heterogeneity of the results reduce the ability to generalize the results. The present study suggests that total sessions and a high risk of bias are associated with heterogeneity, and future analyses should exclude the effects of these factors. The high degree of heterogeneity in this study may also be due to the fact that the outcome is a continuous variable. In general, the degree of heterogeneity tends to be higher in analyses where the outcome is a continuous variable [42]. Since meta-analyses on similar topics have shown a high degree of heterogeneity [6-8, 43], it may be the nature of such studies to be highly heterogeneous. In addition, the funnel plots in this study showed horizontal asymmetry in all sites where BMD was assessed, and publication bias could not be excluded. To eliminate these limitations, it would be desirable to include a larger number of RCTs with a low risk of bias in the analysis.

In conclusion, as a result of the meta-analysis, we found that HLRT led to significant increase in the BMD mainly of the lumbar spine in patients with osteoporosis and osteopenia. With safety assurances and simultaneous improvements in motor function, HLRT may become an effective non-pharmacotherapeutic intervention to increase BMD. However, this meta-analysis has a high degree of heterogeneity and publication bias. It would be necessary to continue accumulating RCTs with a low risk of bias and incorporate their data into the analysis to address the limitations of heterogeneity and publication bias and generalize our findings.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by YK, TW, and HH. HN and MO contributed to the analysis and interpretation of the data in the study. The first draft of the manuscript was written by YK, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgments

We are grateful to Ryoko Ikehara for providing secretarial assistance.

This work was supported by Grants-in-Aid from the Ministry of Health, Labour and Welfare (subject no.:19FA1014) and received funding from Tottori University.

Conflicts of interest

All authors have no conflicts of interest.

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Figure Legends

Fig. 1 Flow diagram of the search process

Fig. 2 Forest plot of meta-analysis results for the lumbar spine

The data are shown as pooled standard mean difference (SMD) with 95% confidence interval (CI) for changes in the intervention and control groups.

Fig. 3 Forest plot of meta-analysis results for the femoral neck (a) and for the total hip (b)

The data are shown as pooled standard mean difference (SMD) with 95% confidence interval (CI) for changes in intervention and control groups.

Fig. 4 Funnel plot of meta-analysis results for the lumbar spine (a), for the femoral neck (b), and for the total hip (c).

The vertical axis represents the standard error and the horizontal axis represents the standard mean difference. The results of each study are plotted.

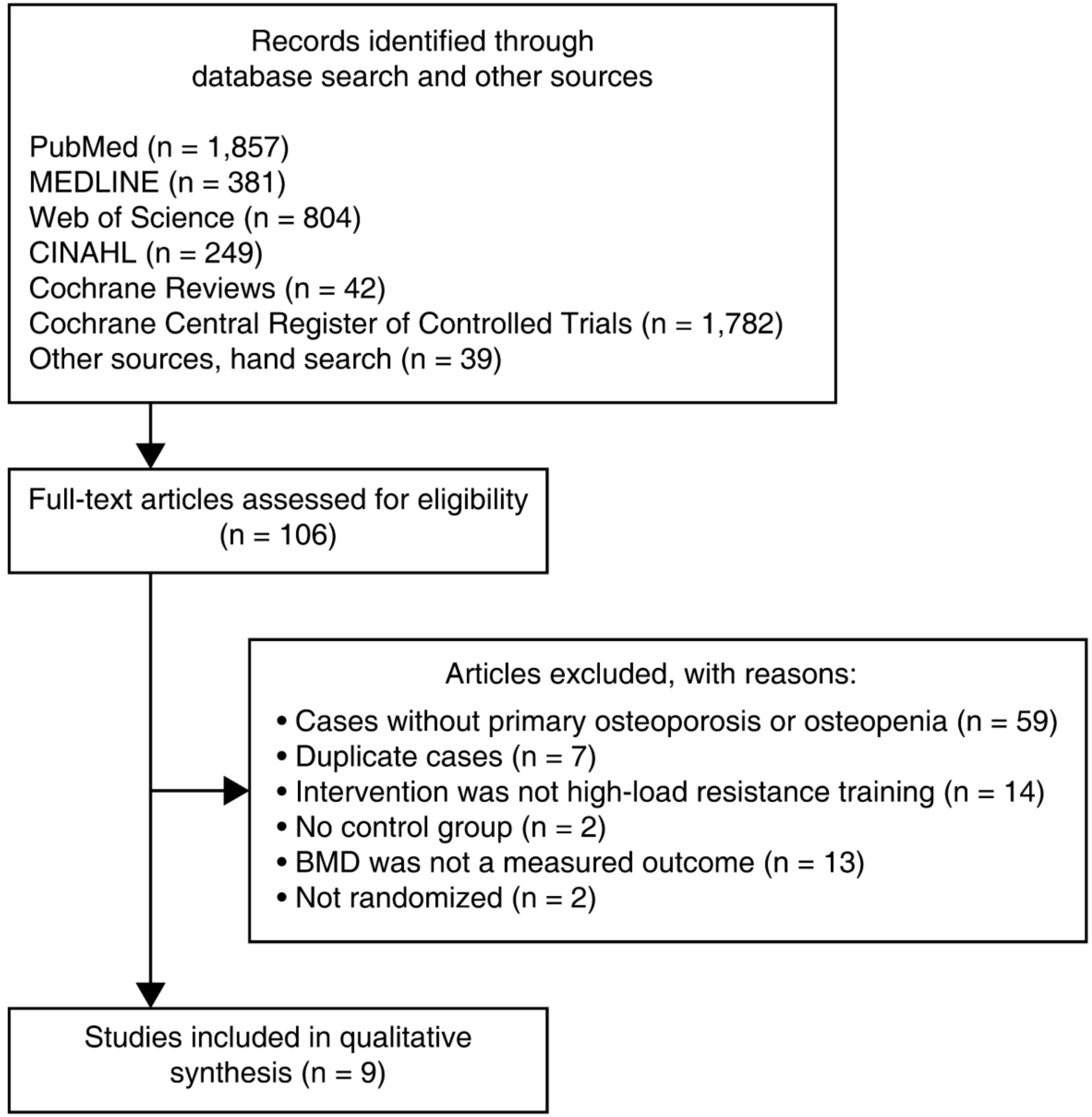

Fig. 1 Flow diagram of the search process

Study or Subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Villareal	-0.01	0.043	65	-0.04	0.035	47	13.8%	0.75 [0.36, 1.14]	2004
Basat	0.012	0.017	11	0.004	0.006	12	12.0%	0.62 [-0.22, 1.46]	2013
Mosti	0.003	0.017	8	-0.008	0.012	8	11.2%	0.71 [-0.31, 1.73]	2013
Hinton	0.016	0.022	19	0.009	0.01	19	12.9%	0.40 [-0.24, 1.04]	2015
Borba-Pinheiro	0.074	0.051	20	0.006	0.007	16	12.3%	1.73 [0.95, 2.51]	2016
Watson	0.023	0.018	43	-0.009	0.014	43	13.4%	1.97 [1.45, 2.49]	2018
Harding	0.042	0.007	34	0.009	0.008	26	11.5%	4.37 [3.42, 5.33]	2020
Kemmler	2.9	7.599	21	-4.1	7.716	22	13.0%	0.90 [0.27, 1.53]	2020
Total (95% CI)			**221**			**193**	**100.0%**	**1.40 [0.68, 2.12]**	

Heterogeneity: $Tau^2 = 0.94$; $Chi^2 = 67.16$, df = 7 (P< 0.00001); $I^2 = 90\%$

Test for overall effect: Z = 3.81 (P = 0.0001)

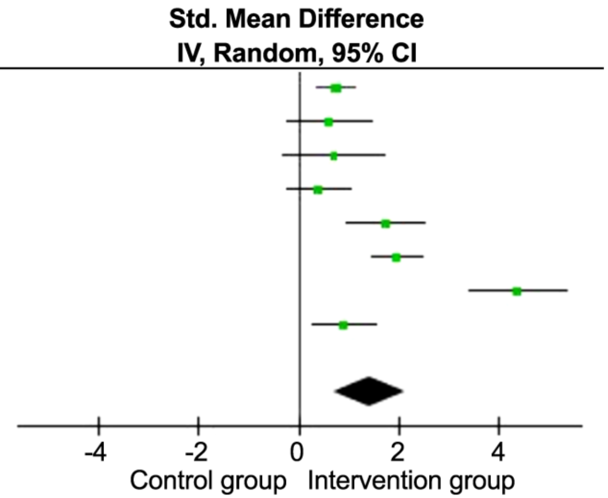

Fig. 2 Forest plot of meta-analysis results for the lumbar spine

The data are shown as pooled standard mean difference (SMD) with 95% confidence interval (CI) for changes in the intervention and control groups.

a

Study or Subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Villareal	0	0.03	65	-0.03	0.026	47	15.7%	1.05 [0.65, 1.45]	2004
Liu-Ambrose	-0.002	0.019	29	0.004	0.021	33	15.4%	-0.29 [-0.80, 0.21]	2004
Mosti	0.004	0.054	8	0.015	0.036	8	13.2%	-0.23 [-1.21, 0.76]	2013
Basat	0.013	0.012	11	0.009	0.012	12	14.0%	0.32 [-0.50, 1.15]	2013
Borba-Pinheiro	0.129	0.031	20	-0.017	0.024	16	10.9%	5.08 [3.67, 6.48]	2016
Watson	0.001	0.012	43	-0.012	0.008	43	15.5%	1.26 [0.80, 1.73]	2018
Harding	0.011	0.006	34	0.012	0.006	26	15.3%	-0.16 [-0.68, 0.35]	2020
Total (95% CI)			**210**			**185**	**100.0%**	**0.86 [0.05, 1.67]**	

Heterogeneity: $Tau^2 = 1.04$; $Chi^2 = 75.53$, df = 6 (P< 0.00001); $I^2 = 92\%$

Test for overall effect: Z = 2.08 (P = 0.04)

b

Study or Subgroup	Intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Liu-Ambrose	0.001	0.021	29	-0.006	0.019	33	15.4%	-0.25 [-0.75, 0.25]	2004
Villareal	0.01	0.028	65	-0.04	0.03	47	15.6%	1.72 [1.28, 2.16]	2004
Mosti	0.005	0.009	8	-0.007	0.008	8	12.5%	1.33 [0.22, 2.45]	2013
Hinton	0.008	0.014	19	-0.005	0.017	19	14.8%	0.82 [0.15, 1.48]	2015
Borba-Pinheiro	0.124	0.03	20	-0.005	0.02	16	11.3%	4.84 [3.48, 6.19]	2016
Kemmler	0	0.013	21	-0.01	0.014	22	15.0%	0.73 [0.11, 1.35]	2018
Harding	0.019	0.006	34	-0.015	0.008	26	15.4%	0.57 [0.05, 1.09]	2020
Total (95% CI)			**196**			**171**	**100.0%**	**1.26 [0.45, 2.08]**	

Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 68.49$, df = 6 (P< 0.00001); $I^2 = 91\%$

Test for overall effect: Z = 3.03 (P = 0.002)

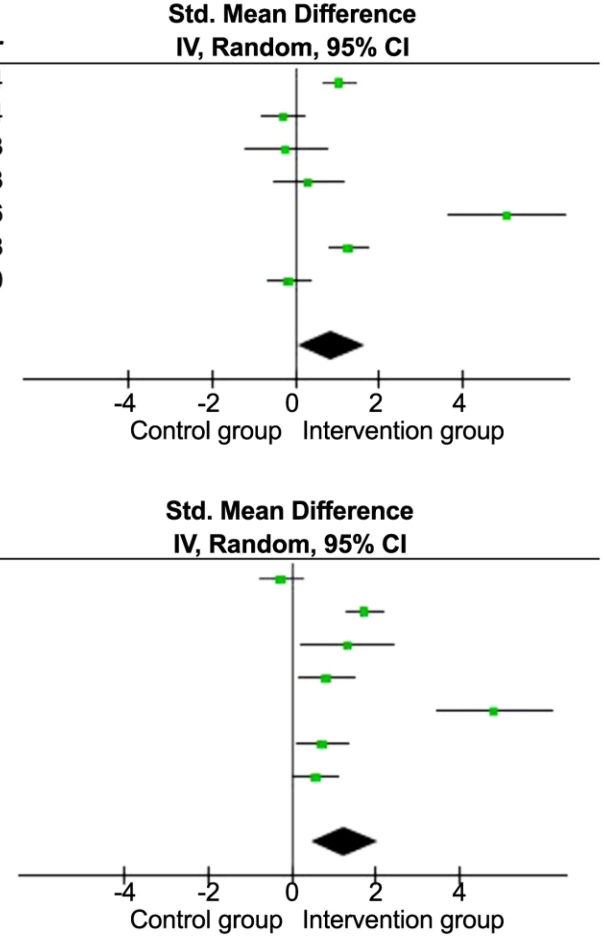

Fig. 3 Forest plot of meta-analysis results for the femoral neck (a) and for the total hip (b)

The data are shown as pooled standard mean difference (SMD) with 95% confidence interval (CI) for changes in intervention and control groups.

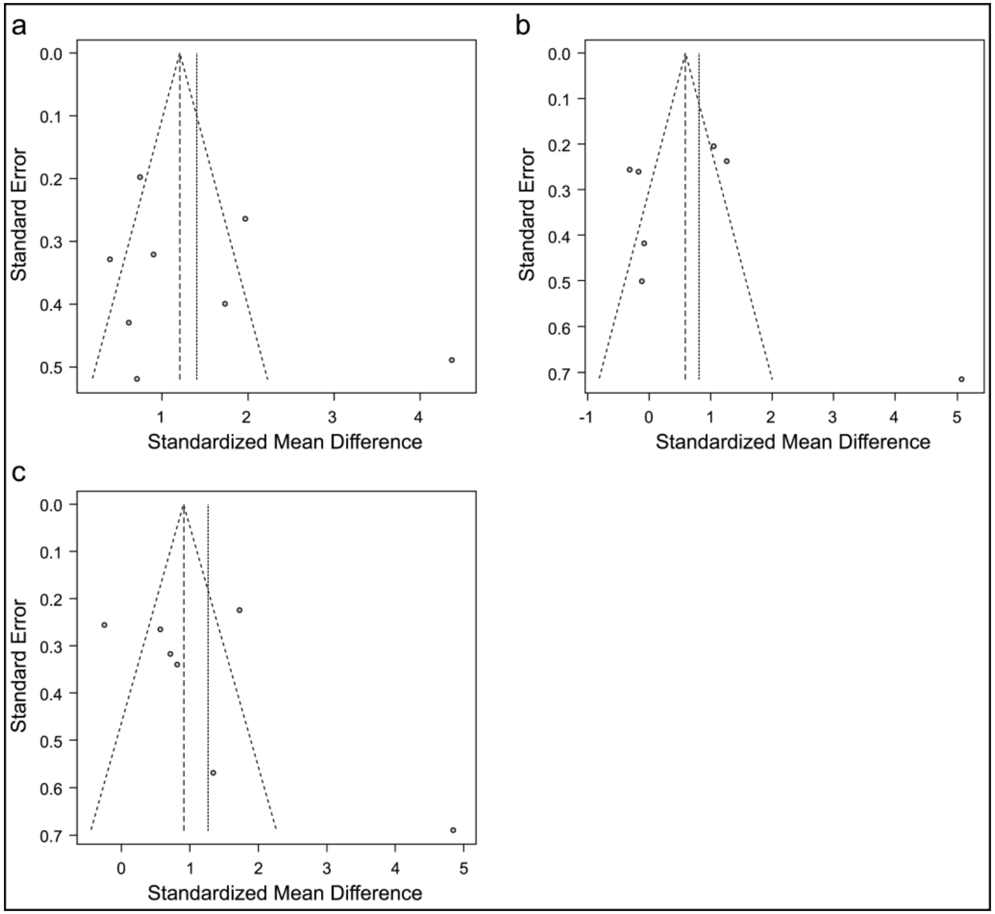

Fig. 4 Funnel plot of meta-analysis results for the lumbar spine (a), for the femoral neck (b), and for the total hip (c).

The vertical axis represents the standard error and the horizontal axis represents the standard mean difference. The results of each study are plotted.

Table 1 Characteristics of included studies

First author, year	Subjects	Basic information of subjects	Details of intervention (menu, frequency)	Details of intervention in CG	Intervention period (weeks)	Measurement device and area of interest	Results	Exercise completion rate	Adverse events
Watson 2018	Women > 58 years old （T-score < −1.0）	IG: 49 subjects, 65.5±5 years old CG: 52 subjects, 65±5 years old	Intensity: A load of 5 sets of 5 repetitions of 80% of one RM adjusted to 85% of one RM Exercises: Deadlift, overhead press, and back squat Frequency: 30-minute sessions, twice a week	Low intensity resistance, balance, and mobility training at home 30-minute sessions, twice a week	32	DXA Lumbar spine Femoral neck	In the CG, lumbar spine, and femur BMD decreased, whereas in the IG, lumbar spine, and femoral neck BMD increased. The IG had increased BMD in all sites measured.	IG: 87.8% CG: 82.7%	One case of mild lower back pain in the IG.

Borba-Pinheiro 2016	Women > 50 years old （T-score < −1.0） Receiving treatment with Alendronate or vitamin D3	IG; 20 subjects, 56.3±5.2 years old CG: 16 subjects, 55.3±6.8 years old	Intensity: Gradual load-elevation from 60% to 90% of one RM Exercises: Leg press using machines, knee extension, plantar ankle flexion, hip abduction, elbow flexion and extension, shoulder abduction Frequency: 60-minute sessions, three times a week	No exercise intervention	52	DXA Lumbar spine Femoral neck Total hip	The effect level was significantly larger than that of the CG.	Not mentioned.	Not mentioned.
Kemmler 2020	Men > 72 years old (T-score < −1.0)	IG: 21 subjects, 77.8±3.6 years old CG: 22 subjects, 79.2±4.7 years old	Intensity: At maximum effort, either 5–7 or 8–10 repetitions Exercises: Leg press, extension, curl, adduction, abduction, latissimus front pulley, rowing, back extension, inverse fly, bench press, military press, lateral raise, butterfly, crunch	No exercise intervention Other: Taking protein, vitamin D supplements and calcium supplements	54	QCT Lumbar spine DXA Total hip	Lumbar BMD was maintained in the IG but was significantly reduced in the CG. There was no significant change in total	95% of the IG completed the exercise program.	There was a report of delayed onset muscle soreness.

			Frequency: Twice a week Other: Taking protein, vitamin D supplements and calcium supplements				hip BMD in both groups.		
Mosti 2013	Women < 75 years old (T-score between −1.5 and −4.0)	IG: 8 subjects, 61.9±5.0 years old CG: 8 subjects, 66.7±7.4 years old	Intensity: Two sets of 8–12 repetitions at approximately 50% of one RM, four sets of 3–5 repetitions at 85–90% of one RM Exercises: Squats with machine Frequency: Three times a week	Exercise for osteoporosis in accordance with guidelines	12	DXA Lumbar spine Femoral neck Total hip	No significant increase in BMD was observed in the IG and CG.	Not mentioned.	Not mentioned.
Hinton 2015	Men 25–60 years old (T-score between −1.0 and −2.5)	IG: 19 subjects, 45.5±9.6 years old CG: 19 subjects,	Intensity: Gradual load elevation from 50% to 90% one RM Exercises: Squats, bent-over rows, modified deadlifts, military presses, lunges, calf raise	Various jump exercises with varying intensities and directions Other: Taking calcium and	48	DXA Lumbar spine Total hip	Lumbar BMD was significantly increased in both groups. Total hip BMD was	IG: 100% CG: 100% There were dropouts unrelated to intervention	There were no adverse events.

		42.1±10.6 years old	Frequency: Twice a week Other: Taking calcium and vitamin D supplements	vitamin D supplements			significantly increased only in the IG.	(IG: 3, CG: 2)	
Harding 2020	Men > 45 years old (T-score < −1.0）	IG: 34 subjects, 64.9±8.6 years old CG: 26 subjects, 67.4±6.3 years old	Intensity: 5 sets of 5 repetitions at 80–85% or higher of one RM Exercises: Deadlifts, squats, over-head press Frequency: 30-minute sessions, twice a week	No exercise intervention	32	DXA Lumbar spine Femoral neck Total hip	In the IG, BMD increased significantly in all sites, and the rates of change were greater than in the CG.	The participation rate of IG was 77.8%, with 3 subjects dropping out for reasons unrelated to the intervention.	Two cases of mild musculoskeletal pain during intervention.

Liu-Ambrose 2004	Women 75–85 years old diagnosed with osteoporosis or osteopenia	IG: 32 subjects, 79.6±2.1 years old CG: 34 subjects, 78.9±2.8 years old	Intensity: Gradual load elevation from 10 to 15 repetitions at 50–60% of one RM to 6–8 reps at 75–85% of one RM Exercises: Biceps curls, triceps extension, seated row, latissimus dorsi pull downs, mini-squats, mini-lunges, hamstring curls, calf raises, and gluteus maximus extensions Frequency: 50-minute sessions, twice a week	Agility training	25	DXA Lumbar spine Femoral neck Total hip	There were no significant changes in the BMD in both groups.	94% completed the intervention The exercise participation rate in IG was 85%.	There were 10 cases of mild musculoskeletal troubles such ass muscle pain during the intervention.
Basat 2013	Post-menopausal women 40–70 years old (T-score between	IG: 11 subjects, 55.9±4.9 years old CG: 12 subjects, 55.6±2.9 years old	Intensity: A 10 RM load according to the ACSM guidelines Exercises: Trunk flexion-extension, hip abduction-adduction, extension, flexion, knee extension-flexion, push-ups	Jump training Other: Taking vitamin D and calcium supplements	24	DXA Lumbar spine Femoral neck	In both groups, the lumbar and femoral neck BMD increased. There was no difference between groups in terms of the	The exercise participation rate of the analyzed subjects was 60% or more.	Not mentioned.

	−1.0 and −2.5）		Frequency: 60-minute session, once a week Other: Taking vitamin D and calcium supplements				amount of change.		
Villareal 2004	Men and women > 78 years old (mean T-score: −1.6) osteopenia: 50%; osteopenic: approx. 30% (Determined to correspo	IG: 65 subjects, 83.0±4.0 years old, women 52% CG: 47 subjects, 83.0±4.0 years old, women 55%	Intensity: 1–2 sets of 6–8 repetitions of each exercise were completed at 65–75% of one RM. This progressed to 3 sets of 8–12 repetitions done at 85–100% of one RM. Exercises: Leg press, knee extension, seated row, upright row, bench press, biceps curl and triceps extension. Frequency: Mean 2.2 sessions per week Other: Taking vitamin D and calcium supplements	Stretching and balance training Other: Taking vitamin D and calcium supplements	36	DXA Lumbar spine Femoral neck	Compared to the CG, the BMD was maintained in the IG, but it was not a significant change.	Deemed favorable, with 94% of analyzed subjects complying with exercise.	24% of subjects dropped out due to medical issues (relation to the intervention is unknown).

nd to inclusion criteria based on subject data, despite there being no description in text)

IG, intervention group; CG, control group; RM, repetition maximal; DXA, dual X-ray absorptiometry; QCT, Quantitative Computed Tomography; ACSM, American College of Sports Medicine

Table 2 Assessment of risk of bias for included studies

First author name, year	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions (effect of assignment to intervention).	Risk of bias due to deviations from the intended interventions (effect adhering to intervention).	Risk of bias due to missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall risk of bias judgement	Comments
Watson 2018	low risk	low risk	low risk	low risk	low risk	low risk	low risk	No particular problem
Mosti 2013	some concerns	some concerns	some concerns	some concerns	low risk	some concerns	high risk	The method of randomization and the effect of dropout cases in the control group are unclear.
Borba-Pinheiro 2016	some concerns	some concerns	some concerns	some concerns	low risk	some concerns	high risk	The method of randomization and the effect of dropout cases in

								the control group are unclear.
Hinton 2015	low risk	low risk	low risk	low risk	low risk	some concerns	some concerns	The consistency between the pre-specified outcome and the outcome described in the paper is unclear.
Harding 2020	low risk	low risk	low risk	low risk	low risk	low risk	low risk	No particular problem
Liu-Ambrose 2004	low risk	some concerns	low risk	some concerns	low risk	some concerns	some concerns	There is a discrepancy between the number of cases with intervention and the number of cases with outcome measures.

Kemmler 2020	low risk	low risk	low risk	low risk	low risk	low risk	low risk	No particular problem
Basat 2013	low risk	some concerns	some concerns	some concerns	low risk	some concerns	some concerns	The effect of dropout cases on the results and the appropriateness of the sample size are unknown.
Villareal 2004	low risk	high risk	high risk	high risk	low risk	some concerns	high risk	Too many dropouts in the intervention group, likely affecting the results

7 **Table 3** Summary of meta–analysis of subgroups and meta-regression

	Study number (included studies)	Number of subjects	SMD (95% CI)	P-value for overall effect	Cochrane Q test (P-value)	I^2 (%)	P-value for meta-regression
Excluded high risk of bias							
Lumbar spine	5 ([15], [16],[17],[30],[32])	IG:128 CG:122	1.62 (0.46–2.78)	P<0.001	56.60 (P<0.001)	93	0.509
Femoral neck	4 ([15],[17][29],[30])	IG:117 CG:114	0.28 (-0.51–1.08)	P=0.48	25.04 (P<0.001)	88	0.119
Total hip	4 ([16],[17],[29],[32])	IG:103 CG:100	0.44 (-0.06–0.95)	P=0.09	9.39 (P=0.02)	68	0.003
Only women							
Lumbar spine	4 ([14], [15],[30],[31])	IG:82 CG:79	1.33 (0.63–2.03)	P<0.001	10.00 (P=0.02)	70	0.439
Femoral neck	5 ([14], [15],[29],[30],[31])	IG:111 CG:112	1.11 (-0.15–2.37)	P=0.08	62.05 (P<0.001)	94	0.457
Total hip	3 ([14],[29], [31])	IG:57 CG:57	1.92 (-0.86–4.70)	P=0.18	50.10 (P<0.001)	96	0.273
Only men							
Lumbar spine	3 ([16], [17],[32])	IG:74 CG:67	1.86 (-0.21–3.93)	P=0.08	48.67 (P<0.001)	96	0.439
Femoral neck	1 ([17])	IG:34 CG:26	-0.16 (-0.68–0.35)	P=0.53	Not applicable	Not applicable	0.457

Total hip	3 ([16], [17],[32])	IG:74 CG:67	0.68 (0.34–1.02)	P<0.001	0.36 (P=0.84)	0	0.273
Elderly							
Lumbar spine	5 ([14], [15],[17],[28],[32])	IG:171 CG:146	1.70 (0.65–2.76)	P=0.002	56.51 (P<0.001)	93	0.859
Femoral neck	5 ([14], [15],[17],[28],[29])	IG:179 CG:157	0.36 (-0.34–1.06)	P=0.31	35.75 (P<0.001)	89	0.136
Total hip	5 ([14], [17],[28],[29],[32])	IG:157 CG:136	0.80 (0.03–1.57)	P=0.04	35.32 (P<0.001)	89	0.373
Middle aged							
Lumbar spine	3 ([16], [30],[31])	IG:50 CG:47	0.90 (0.09–1.72)	P=0.03	7.04 (P=0.03)	72	0.859
Femoral neck	2 ([30],[31])	IG:31 CG:28	2.66 (-2.00–7.32)	P=0.26	32.70 (P<0.001)	97	0.136
Total hip	2 ([16],[31])	IG:39 CG:35	2.78 (-1.16–6.72)	P=0.17	27.29 (P<0.001)	96	0.373
Total sessions high							
Lumbar spine	6 ([15],[16],[17],[28][31],[32])	IG:202 CG:173	1.63 (0.75–2.52)	P<0.001	63.95 (P<0.001)	92	0.932
Femoral neck	4 ([15], [17],[28],[31])	IG:162 CG:132	1.59 (0.42–2.76)	P=0.008	53.31 (P<0.001)	94	<0.001
Total hip	5 ([16], [17],[28],[31],[32])	IG:159 CG:130	1.56 (0.65–2.47)	P=0.001	42.24 (P<0.001)	91	0.005

Total sessions low							
Lumbar spine	2 ([14],[30])	IG:19 CG:20	0.65 (0.00–1.30)	P=0.05	0.02 (P=0.89)	0	0.932
Femoral neck	3 ([14], [29],[30])	IG:48 CG:53	-0.14 (-0.54–0.25)	P=0.47	1.60 (P=0.45)	0	<0.001
Total hip	2 ([14], [29])	IG:37 CG:41	0.46 (-1.08–2.00)	P=0.56	6.42 (P=0.01)	84	0.005
Control group with exercise intervention							
Lumbar spine	5 ([14], [15],[16],[28],[30])	IG:146 CG:129	0.92 (0.30–1.53)	P=0.003	19.38 (P<0.001)	79	0.061
Femoral neck	5 ([14], [15],[28],[29],[30])	IG:156 CG:143	0.47 (-0.20–1.15)	P=0.17	27.78 (P<0.001)	86	0.110
Total hip	4 ([14], [16],[28],[29])	IG:121 CG:107	0.89 (-0.15–1.92)	P=0.09	34.17 (P<0.001)	91	0.338
Control group with no exercise intervention							
Lumbar spine	3 ([17],[31],[32])	IG:75 CG:64	2.31 (0.41–4.20)	P=0.02	35.56 (P<0.001)	94	0.061
Femoral neck	2 ([17],[31])	IG:54 CG:42	2.41 (-2.72–7.55)	P=0.36	47.15 (P<0.001)	98	0.110
Total hip	3 ([17],[31],[32])	IG:75 CG:64	1.90 (0.15–3.65)	P=0.03	34.20 (P<0.001)	94	0.338

IG; intervention group, CG; control group, SMD; standardized mean difference, CI; confidence interval

Elderly: mean age of the intervention group was 60 years or older, Middle-aged: mean age of the intervention group was less than 60 years, Total session high; intervention frequency × duration greater than the median (64 sessions) of the selected articles, Total sessions low; intervention frequency × duration less than to the median (64 sessions) of the selected articles

P-value for meta-regression of Only men and Only women, Elderly and Middle age, Total sessions low and Total sessions high, Control group with exercise intervention and Control group with no exercise have the same values as we used the same variable.

Electronic supplementary material

Article title: Impact of high-load resistance training on bone mineral density in osteoporosis and osteopenia: a meta-analysis

Journal: Journal of Bone and Mineral Metabolism

Authors: Yuki Kitsuda[1)], Takashi Wada[1)], Hisashi Noma[2)], Mari Osaki[1)], Hiroshi Hagino[1,3)]

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Online Resource. Database search strategy

PubMed, 2020/6/14

♯	Search formula	number of hits
1	osteoporosis [MeSH Terms]	55,448
2	osteopenia [MeSH Terms]	76,122
3	menopause [MeSH Terms]	56,814
4	#1 or #2 or #3	127,463
5	"high intensity"	28,779
6	loading	260,656
7	exercise	458,954
8	resistance	1,148,838
9	strength	365,497
10	"heavy weight"	384
11	training	1,892,349
12	"weight lifting"	5,117
13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	3,798,990
14	#4 and #13	19,049
15	#14 Filters: Randomized Controlled Trial	1,857

Cochrane Library, 2020/6/14

♯	Search formula	number of hits
1	MeSH descriptor: [osteoporosis] explode all trees	4,072
2	MeSH descriptor: [bone diseases, metabolic] explode all trees	4,611
3	MeSH descriptor: [menopause] explode all trees	6,839
4	"high intensity"	6,898
5	loading	12,179
6	exercise	95,346
7	resistance	57,841
8	strength	36,566
9	"heavy weight"	47
10	training	88,788
11	"weight lifting"	1,173
12	#1 or #2 or #3	10,829
13	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	221,293
14	#12 and #13	Cochrane reviews: 42 CENTRAL: 1,782

Web of Science, 2020/6/14

♯	Search formula	number of hits
1	osteoporosis	91,123
2	osteopenia	11,278
3	menopause	30,904
4	#1 or #2 or #3	121,729
5	“high intensity”	52,745
6	loading	1,308,992
7	exercise	455,895
8	resistance	1,570,688
9	strength	1,150,437
10	“heavy weight”	1,222
11	training	927,691
12	“weight lifting”	1,078
13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	4,936,829
14	#4 and #13	17,855
15	#14 and “randomized controlled trial”	804

CINAHL and MEDLINE, 2020/6/15

♯	Search formula	number of hits
1	(MH “osteoporosis”)	24,024
2	osteopenia	2,819
3	(MH “menopause”)	8,869
4	#1 or #2 or #3	33,829
5	“high intensity”	8,676
6	loading	19,597
7	exercise	194,555
8	resistance	124,902
9	strength	95,187
10	“heavy weight”	94
11	training	235,123
12	“weight lifting”	3,389
13	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12	584,623
14	#4 and #13	4,321
15	#14 Filters: randomized Controlled Trial	CINAHL: 249 MEDLINE: 381