Health related quality of life in older people with osteoporotic vertebral fractures: a systematic review and meta-analysis

Authors
Usama A. Al-Sari[1]
Jonathan Tobias[2]
Emma Clark[3]

The affiliations and address of the authors
University of Bristol/ Musculoskeletal Research Unit

[1]PhD student, Academic Rheumatology, Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Southmead Hospital, Westbury-on-Trym, Bristol. BS10 5NB
Ua14948@bristol.ac.uk

[2]Professor of Rheumatology, Academic Rheumatology, Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Southmead Hospital, Westbury-on-Trym, Bristol. BS10 5NB
Jon.Tobias@bristol.ac.uk

[3]Consultant Senior Lecturer in Rheumatology, Academic Rheumatology, Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Southmead Hospital, Westbury-on-Trym, Bristol. BS10 5NB
Emma.Clark@bristol.ac.uk

Corresponding Author: Emma Clark
Academic Rheumatology, Musculoskeletal Research Unit, School of Clinical Sciences, University of Bristol, Southmead Hospital, Westbury-on-Trym, Bristol. BS10 5NB
Telephone: +44 (0) 117 414 7841
Fax: +44 (0) 117 414 0570
Email: Emma.Clark@bristol.ac.uk

Conflicts of interest Usama A Al-Sari, Jonathan H Tobias, and Emma M Clark declare that they have no conflict of interest.

Abstract

Purpose: This meta-analysis was conducted to identify if there are any differences between physical and/or mental health related quality of life (HRQoL) in older people with osteoporosis based on conventional T score definitions, and the presence or absence of vertebral fracture.

Methods: A comprehensive search was undertaken using the databases of PubMed, Embase, Medline, Web of Science, and the "grey" literature from 1950 to the end of April 2015. Search terms for vertebral fracture (VF) included VF, osteoporotic fracture, fragility fracture, and spinal fracture. Quality of life was searched using the following terms: quality of life, health related quality of life, HRQoL, and QoL. Strict inclusion and exclusion criteria were used. The standardized mean difference (SMD) was calculated for each HRQoL domain by the difference in means between case and control groups divided by the pooled SD of participants.

Results: 16 eligible studies were identified involving 3131 men and women. There was evidence of publication bias and heterogeneity. The meta-analysis showed worse physical (SMD= 0.53, 95% confidence interval (CI) 0.38 to 0.68; P <0.001) and mental (SMD= 0.19, 95%CI 0.05 to 0.33; P= 0.009) HRQoL in osteoporotic older people with vertebral fracture compared to those without fracture. Similar differences were observed for physical HRQoL in further analyses accounting for possible confounding effects of age. Sub-analysis to assess associations between number/severity of fractures and time since fracture were not possible due to small numbers of studies that accounted for age.

Conclusion: Osteoporotic older people with vertebral fracture have worse physical HRQoL than osteoporotic older people without vertebral fracture, even after accounting for age differences.

Keywords

Osteoporosis

Quality of life

Vertebral fracture

Physical health

Mental health

Mini-abstract

Health related quality of life in osteoporotic patients with vertebral fracture is of increasing interest, but relevant studies have yielded debatable results. This systematic review and meta-analysis of 16 observational studies demonstrates a clear association between physical health status and presence of vertebral fracture after accounting for age.

INTRODUCTION

Vertebral fractures are strong independent risk factor for further fractures. In one systematic review, the risk factor for having a new vertebral fracture in women that have already fractured one vertebra was 4.4 times higher than those without fracture [1]. Moreover, prior vertebral fracture was also a good predictor for hip, forearm and any other non-vertebral fractures. Vertebral fracture may also lead to back pain, spinal deformity, short stature, decreased mobility and physical performance, social isolation, lack of self-confidence, and depression [2, 3]. However, the impact of vertebral fracture on quality of life is less clear. Osteoporosis, which underlies many cases of vertebral fractures, as well as increasing the risk of fractures at other sites, is recognised to have a negative impact on quality of life.

Health Related Quality of Life (HRQoL) is the term that covers health related physical, emotional, psychological and social wellbeing and how disease or treatments can effect these parameters [4]. HRQoL has become an important patient-related outcome for assessing the impact of interventions in a wide range of diseases including osteoporosis. Two types of instruments to measure HRQoL are available: generic and disease-specific instruments, and both types tend to divide HRQoL into effects on physical and mental functioning (domains). Examples of generic questionnaires typically used to evaluate HRQoL in osteoporosis are the short form (for example, SF-12[5]) and the EuroQol five dimensions questionnaire (EQ-5D)[6]. More recently, osteoporosis-specific questionnaires have been developed such as the Quality of Life Questionnaire, issued by the European Foundation for Osteoporosis (QUALEFFO)[7].

It is recognised that osteoporosis itself can have a negative impact on HRQoL. For example, a systematic review of 27 papers covering the osteoporosis literature from 1950 to 2012 [8] identified that osteoporosis itself can have a negative impact on HRQoL. In 13 papers HRQoL was reported separately in those with and without vertebral fractures: six papers reported worse quality of life in those with vertebral fracture, five reported no difference, and in two studies only some domains of the HRQoL tools were worse in those with vertebral fracture. However, no meta-analysis was carried out.

Although the above studies suggest that vertebral fractures may have an adverse on HRQoL, no meta-analysis was carried out and so it is difficult to estimate the size of effect. Moreover, although there is some suggestion that vertebral fracture selectively affects certain domains of HRQoL, this has not been examined in detail. In addition, associations between vertebral fractures and HRQoL could reflect confounding by age and other factors which previous papers have only examined to a variable extent. It is important to identify if vertebral fractures *per se* are associated with reduced HRQoL because this would justify targeting of interventions aimed at improving quality of life to this group, for example physiotherapy to improve physical functioning, or psychological intervention to improve mental functioning.

Therefore the aims of this study are to provide an up to date synthesis of the literature in order to (1) determine whether vertebral fractures adversely impact HRQoL in older people, (2) estimate the size of any reduction observed, (3) establish whether any specific domain(s) are preferentially reduced and (4) explore whether any association which is observed is likely to reflect confounding by age. So as to distinguish effects of vertebral fracture from those of underlying osteoporosis, we restricted our analyses to studies of patients with osteoporosis (as defined by T score < -2.5), where analyses had been performed separately in those with and without vertebral fractures.

METHODS

Inclusion criteria

All studies that estimated the association between vertebral fractures and HRQoL in osteoporotic men and women aged ≥50 years were included. Osteoporosis was defined as low BMD (T score <-2.5) either for lumbar or femoral neck by any standard imaging modality. All studies were required to have extractable information about physical and mental components of quality of life measured by any generic or osteoporosis specific validated HRQoL instrument.

Exclusion criteria

Articles were excluded if (1) data on men and women aged ≥ 50 years could not be extracted, (2) if data on those with osteoporosis could not be extracted, (3) if there was no control group without vertebral fractures, (4) if insufficient data was available, or (5) they were written in a language that could not be translated: those written in English, French, Spanish, Ukraine, Russian, Turkish and Lithuanian could be translated by the research team.

Search strategy

A systematic strategy was conducted to search electronic databases and identify published work using both medical subject headings (MeSH) and free-text words. In addition to the computerized searching, related print journals were hand searched, and citations lists of relevant studies were reviewed. The search was carried out in April 2015 and used all available dates up to search time. The database searched were PubMed, Embase, Medline, Web of Science, and the Cochrane Library as well as the 'gray' literature. We used the following terms to identify fracture, (vertebral fracture, osteoporotic fracture, fragility fracture, and spinal fracture). Quality of life was searched using the following terms, (quality of life, health related quality of life, HRQoL, and QoL).

The retrieved studies were evaluated in three stages. In the first stage (See Fig 1), any study with unfit title or unrelated abstract was excluded. Then, in the second stage, full texts of the remaining studies were read and evaluated to exclude studies that were not suitable. Finally, we excluded any article that did not identify osteoporosis using our pre-specified definition involving a T score. Articles also excluded if they did not have relevant extractable data (physical and mental domains of HRQoL), were duplicated or could not be translated (article in Serbian). The authors were contacted if the studies did not include sufficient information.

Assessment of methodological quality

As there is no standard quality scale that incorporates all the important criteria for studies assessing the association between vertebral fracture and HRQoL we evaluated the methodological quality of studies according to the presence of absence of (1) a clear definition for osteoporosis, (2) a clear definition for vertebral fracture, (3) clearly stated inclusion criteria, (4) clearly stated exclusion criteria, (5) taking into account number of vertebral fractures or assessment of a dose response relationship between HRQoL and number of vertebral fractures, (6) clearly identified time since the last fracture, (7) clearly stated HRQoL outcome of interest, (8) clear information about the study population setting, and (9) accounting for age. One score was given for each one of these criteria with total score of nine for all.

Statistical analysis

HRQoL scales were standardised by (1) ensuring uniformity of direction of scale, and by (2) calculating the standardized mean difference (SMD) for each domain by the difference in means between case and control groups divided by the pooled SD of participants [9]. Mean and SD were calculated for studies that reported differences in median (range) using a standard technique [10]. The effect size of the SMD was classified as a large effect if the SMD ≥ 0.8, moderate if between 0.5 to < 0.8, and small if between 0.2 to <0.5, according to Cohen definition [11]. A funnel plot was drawn to test the publication bias, while heterogeneity among the studies was tested using random-effects (assuming that the true effect could vary from study to as different instruments were used which may have varying sensitives to the impact of vertebral fractures) and I^2 statistic. The percentage of variation was reported using recommendations from Higgins [12]: low effect of heterogeneity if $I^2 <25\%$, moderate if I^2 25%-75%, and high effect of heterogeneity if $I^2 >75\%$. Analysis was by using Stata vs13 software applying the “metan” and “funnel” commands. Sensitivity analyses were performed by stratifying analyses by whether differences in age group had been reported in the published paper to classify all identified papers into (1) those where no differences in age was seen in those with and without vertebral fractures; (2) a difference in age was reported with people with vertebral fractures being older; and (3) those papers where age was not reported. In addition, stratified analyses were undertaken to assess the impact of pain, by limiting secondary meta-analyses to those papers where no differences in pain were reported between those with and without vertebral fracture.

RESULTS

Description of studies identified

2504 studies were identified; 2339 studies were excluded in the first exclusion stage, and 115 studies were excluded after reading the full papers in the second stage (See Figure 1). 50 full text papers were retrieved in the final stage, of these 34 were excluded: 3 because they defined osteoporosis as simply 'low BMD' without T scores, or by presence of radiographic vertebral fracture; 10 studies due to unavailable data about physical or mental HRQoL; 16 studies because they evaluated utility (by EQ-5D which does not have separate physical and mental domains); 4 because of duplicated data; and one Serbian study because it was unable to be translated.

Sixteen studies that met all inclusion criteria were included in the final analysis [13-28] with a total of 3131 men and women (1698 with vertebral fracture, and 1433 without vertebral fracture). Fourteen of these studies were cross-sectional [13-17, 19, 20, 22-28], one case-control [21], and one baseline data from an RCT [18]. The characteristics of the included studies are shown in Table 1. To measure bone density, DXA was used in all the included studies. Osteoporosis was defined as T score ≤ 2.5 SD, and lumbar BMD was measured in five studies [19-22, 24], eight studies reported lumbar or/and hip BMD [13, 16-18, 23, 25, 27, 28], and in three studies the site of DXA scan was not mentioned [14, 15, 26]. Vertebral fractures were identified using Semi-quantitative (SQ) method in 11 studies [13, 16, 17, 21-25, 27, 28], quantitative morphometric (QM) method in two studies [14, 19], the SQ, the binary semi quantitative (BSQ), and the QM in one study, the Japanese diagnostic criteria in one study [26], and in one study the method is not mentioned [15]. The number of participants with vertebral fracture in each study ranged from 9 [28] to 548 [17]. Eleven studies excluded patients with malignancy. The number of controls without vertebral fracture ranged from 19 [26] to 302 [18].

Six papers reported HRQoL by using the (QUALEFFO) questionnaire [17, 19, 20, 22, 23, 25], three used the (SF-36) questionnaire [14, 15, 28], one used the generic SF-12 [16], one used both QUALEFFO and SF-36 [27], one used SF-36, mini-osteoporosis quality of life questionnaire (OQLQ) and the generic (EQ-5D) [13], one used QUALEFFO and EQ-5D [21], one used QUALEFFO and the World Health Organization Quality of Life questionnaire (WHOQOL-100) [24], one used the generic Nottingham health profile questionnaire (NHP), EQ-5D and QUALEFFO [18], and one used SF-36, the Japanese Osteoporosis Quality of Life Questionnaire (JOQOL), and EQ-5D [26]. The effect size between groups was reported as mean (SD) in all studies apart from

Lombardi study [14] which reported effect in median (range). In the combined 16 studies, 2252 participants had HRQoL assessed by QUALEFFO, 654 by SF-36 and 225 by SF-12. In the QUALEFFO pain was assessed by asking about amount and severity of back pain. In the SF-36 pain was assessed by asking about the amount of body pain and its impact on normal work.

In 13 studies patients were recruited from secondary care [14, 15, 17-19, 21-28], one study recruited patients from primary care [20], one study from both secondary and primary care [13], and one was a population-based study [16]. In 11 studies the age for those with and without vertebral fractures were reported [13, 14, 16-18, 21-23, 25, 27, 28]. For these studies, and where data on age was available, the mean age for cases was 70.3 ± 6.6 years and for controls was 66.5 ± 7.6 years. Five studies reported the mean age of the whole sample [15, 19, 20, 24, 26], and combined this was 64.7 ± 7.8 years. Within all 15 studies, the age for the combined patients was 68.0 ± 7.4 years. For the five studies that reported no difference in age the mean age for cases was 70.66 ±1.47 while for controls the mean age was 68.12 ±2.83 [13, 14, 17, 22, 28]. Apart from Demirdal study that included a small number of men, all the studies recruited only women.

Study Quality

One study met all our qualitative study quality criteria with a total score of nine out of nine – see Appendix [13]. Five studies scored eight: two did not report time since fracture [22, 28], and three did not take into account age as a confounder [20, 23, 27]. Nine studies missed two criteria and scored with seven. The missed criteria were both time since the fracture and not taking into account age as a confounder for six studies [16, 18, 19, 24-26]. One did not report both time since fracture and did not take into account number of vertebral fracture [14]. One did not report time since the fracture and lacked clearly stated exclusion criteria [17], and one did not take into account number of vertebral fracture nor the age as a confounder [21]. Finally, one study scored six as it lacked a clear definition for vertebral fracture, reported time since fracture, and didn't take account of age as a confounder [15]. A funnel plot for HRQoL was drawn to test the publication bias and revealed asymmetry for the studies with a moderate degree of heterogeneity (I^2 61.7%).

Physical domain of HRQoL

Overall, nine studies from the total 16 found an association between presence of a vertebral fracture and reduced physical domain of HRQoL [13, 16-18, 20, 21, 23, 25, 27], while in seven studies there was no association identified [14, 15, 19, 22, 24, 26, 28]. After pooling all 16 studies, participants with vertebral fracture had approximately half an SD lower physical-related HRQoL compared to those without vertebral fracture (SMD=0.53, 95% confidence interval (CI) 0.38 to 0.67, P <0.001).

Sensitivity analyses

To explore the potential confounding effect of age on QoL, studies were stratified into three groups (A) those that reported a difference in age with cases being older, (B) those where age was not reported separately for cases and controls, and (C) those were cases and controls were the same age. Reduced physical HRQoL was seen in all three subgroups: SMD=0.70, 95% CI 0.50 to 0.90, P<0.001 for those where cases were older, SMD=0.34, 95% CI 0.10 to 0.59, P=0.005 for those were age was not mentioned, and SMD=0.39, 95% CI 0.06 to 0.73, P=0.023 for those were the cases and controls were of the same age. (See Fig 2).

To explore the role of pain as a mediator of the association between vertebral fractures and HRQoL, the meta-analysis was repeated using the four studies that reported no difference in both age and pain between osteoporotic patients with and without vertebral fracture. A reduction in physical HRQoL was observed in vertebral fracture patients, although the magnitude of this decrease was slightly smaller than that seen in those studies matched for age alone (SMD=0.25, 95% CI 0.02 to 0.49, P=0.032) (See Fig 3).

Mental domain of HRQoL

Overall, four studies found an association between presence of a vertebral fracture and reduced mental-related HRQoL [13, 21, 25, 27] while in the remaining 12 studies no association was identified. After pooling all 16 studies, the SMD in the mental domain of HRQoL between participants with and without vertebral fractures was 0.20, 95%CI 0.06 to 0.34, P=0.005. However, after limiting the meta-analysis to those studies with no difference in age in cases and controls, no difference in mental HRQoL was seen (SMD=0.04, 95% CI -0.32 to 0.41, P<0.822) (See Fig 4).

DISCUSSION

We present the results from the first systematic review and meta-analysis of HRQoL in osteoporotic patients with and without vertebral fractures. Our results show that osteoporotic patients with vertebral fractures have moderately reduced physical health status compared to osteoporotic patients without vertebral fracture.

A previous systematic review has highlighted that osteoporosis itself can have a negative effect on HRQoL [8]. We extend these findings by showing that within the population of people with osteoporosis, the presence of a vertebral fracture is associated with worse physical functioning compared to those that have not fractured. We also identified a small reduction in mental health status in osteoporotic people with vertebral fractures compared to those without vertebral fractures, but this difference was no longer observed when analyses were restricted to age matched studies. Previous studies have shown that mental HRQoL reduces with increasing age [29].

In contrast, the reduction in physical HRQoL in patients with vertebral fractures was also observed in age-matched studies, suggesting this relationship is not solely a result of confounding by age. However, there is only a limited ability in meta-analyses to look at the role of confounding, and there may still be residual confounding by age. Furthermore, we were unable to look at other potential confounders that may influence vertebral fracture risk and quality of life measures such as smoking, glucocorticoid use or others. Alternative study designs such as prospective cohort studies are required to assess the impact of other potential confounders such as these on the association between vertebral fractures and reduced physical quality of life. Nonetheless, our analysis stratified by age, does suggest an association between the presence of an osteoporotic vertebral fracture and reduced physical domain of HRQoL. Because only five studies had age-matched vertebral fracture cases and controls, this made further sub-analyses of the association between the number and severity of vertebral fractures, and time since fracture and HRQoL impossible. This is an important limitation of the current literature.

Our results also show, for the first time, that the reduction in the physical domain of HRQoL in osteoporotic people with vertebral fractures compared to those without fracture was not fully explained by pain. This reduction in physical HRQoL in people with vertebral fractures but no pain is biologically plausible, perhaps due to physical limitation associated with changed spinal morphology such as increased kyphosis. In addition, it is well recognised that osteoporotic vertebral fractures can result in musculoskeletal, respiratory and postural abnormalities, potentially independent of pain. All these burdens can lead to a notable decline in the individual’s quality of life, either directly by the effect on the person's daily activities and physical performance, or indirectly by the fear of falling and the fear of additional fractures. This has important implications for targeting of interventions to improve quality of life in people with vertebral fractures, as our results demonstrate that vertebral fracture can cause physical limitations even in the absence of pain. Our results suggest that all people with vertebral fractures should be offered tailored interventions to increase physical functioning, and some should additionally be offered interventions to reduce pain.

Alternatively, the reduced physical health status in those with vertebral fractures may reflect poorer general health status, for example higher comorbidities, than a consequence of the vertebral fracture itself. The majority of included studies were cross-sectional in nature, with the identification of the presence of a vertebral fracture occurring at the same time as the HRQoL measure. It is therefore possible that the people with vertebral fractures had reduced physical HRQoL prior to their vertebral fracture. We tried to account for frailty by stratification by age adjustment, but it is likely that residual confounding remains.

Despite the meta-analysis showing an overall reduction in the physical domain of HRQoL in osteoporotic people with vertebral fractures compared to those without, there was considerable variability between studies. The reported mean differences for the physical domain of HRQoL ranged from zero [14, 19] to 19 [21]. These variations are likely to be explained by the characteristics of the study participants. For example, in one study from Brazil [14] that reported no difference in the physical health, only physically fit participants were included. In the study that presented the largest difference in physical domain of HRQoL, over half the cases had more than one vertebral fracture [21].

The exact components of physical activity, activities of daily living, movement, exercise or sport that contribute to the physical domain of HRQoL are unknown, and further work is required to help guide best management. For example, the questions within the SF36 which contribute to the physical domain ask participants to rate their current ability to wash, dress, bend, lift, climb, walk and do moderate/vigorous activity. Within the QUALEFFO the physical domain questions ask about washing, dressing, lifting and bending, and also about housework, cooking, shopping, climbing stairs, kneeling down, sporting activities and gardening. It would be useful to know if all these aspects of physical functioning are reduced in people with vertebral fractures, or only a few components which could be targeted by interventions.

The methodological quality of the studies included in this review were variable, with potential for bias and confounding, as all the studies were observational. In particular, only a minority of studies accounted for age, an important confounder of HRQoL. Unclear reporting of the time between occurrence of the vertebral fracture and assessment of HRQoL may have introduced bias and would tend to move the observed association closer to the null. The majority of our studies were cross-sectional in design, and this may have introduced bias through recruitment strategies which may affect generalisability. Lack of representativeness of the control selection in the case control studies is unlikely to have introduced bias as we limited studies to those that only recruited osteoporotic people. In addition, a moderate degree of heterogeneity was reported among the included studies, suggesting our results should be interpreted with some caution. Evidence of publication bias was seen, despite including non-English studies in this analysis, and is likely to be due to unpublished small studies with negative results. However, as most included articles scored seven or more out of nine on our methodological quality indicators, the addition of missing small negative studies is likely to be minimal. In addition, only one study included men, so generalisability may be affected. Finally, due to manpower constraints, the selection of studies was not performed by two independent reviewers, as proposed by PRISMA, and this is a weakness of this study.

In conclusion, we present the results of the first meta-analysis of HRQoL in osteoporotic patients with and without vertebral fractures, and show that physical health status is lower in those with vertebral fractures. This has important implications for targeting of interventions to improve quality of life in people with vertebral fractures, as our results demonstrate that vertebral fracture can cause physical limitations regardless of age and pain. In addition, we highlight important area for future research: age and pain must be accounted for; men are under-studied; and research is needed to assess the effect of potential confounders such as smoking and glucocorticoid use. Further understanding of exactly what physical functioning is impaired in people with osteoporotic vertebral fracture would allow development of appropriate interventions to improve quality of life.

FIGURE LEGENDS

Figure 1: Flow diagram based on PRISMA recommendations illustrating the identification and selection of articles for review.

Figure 2: Forest plots showing the meta-analyses for osteoporotic patients with and without vertebral fracture for the physical health related quality of life (HRQoL), grouped according to information available on age (A) Differ in age: cases older, (B) Difference in age not reported, and (C) Cases and controls at the same age. Results are reported as standardised mean differences (SMD) and 95% confidence intervals (CI).

Figure 3: Forest plot showing the meta-analyses for osteoporotic patients with and without vertebral fracture for the physical health quality of life (HRQoL) utilizing only those studies that reported no differences in age and pain in cases and controls. Results are reported as standardised mean differences (SMD) and 95% confidence intervals (CI).

Figure 4: Forest plots showing the meta-analyses for osteoporotic patients with and without vertebral fracture for the mental health related quality of life (HRQoL), grouped according to information available on age (A) Differ in age: cases older, (B) Difference in age not reported, and (C) Cases and controls at the same age. Results are reported as standardised mean differences (SMD) and 95% confidence intervals (CI).

Table 1: Description of studies that have been included in this systematic review of health-related quality of life (HRQoL) in osteoporotic men and women >50 years of age with and without vertebral fractures (VF).

Study	Study population	Additional differences between (VF) and (non-VF) patients	Vertebral fracture case definition	HRQoL tools	Results *Mean difference (95%CI of difference)
Cross-sectional studies					
Salaffi et al. (2007) Italy	Primary care centres and hospital outpatient clinics n without VFs = 244 n with VFs =234 mean age= 68.5 ± 7.8	No difference in age, BMI, menopause time, Education level, but differ in No. of comorbidity conditions	SQ	SF-36 mini-OQLQ EQ-5D	Physical function= 8.01 (6.21 to 9.80) Mental function= 3.35 (1.73 to 4.97)
Yilmaz et al. (2008) Turkey	Physical Therapy and Rehabilitation Polyclinic of Hospital n without VFs = 36 n with VFs = 10 mean age= 63.2 ± 9.5	Difference between groups not mentioned	Medical files examined	SF-36	Physical function= No difference seen Mental function= No difference seen
Sanfelix et al. (2011) Spain	A population-based study n without VFs = 168 n with VFs = 57 mean age= over 50	Difference in age	SQ	SF-12	Physical function= 4.34 (1.31 to 7.37) Mental function= No difference seen
Fechtenbaum et al. (2005) France	Data from rheumatologist report n without VFs = 40 n with VFs = 548 mean age= 71.6 ± 5.0	No difference in age, BMI, menopause, peripheral fracture, and anti-osteoporotic treatment	SQ	QUALEFFO	Physical function= 6.47 (1.09 to 11.84) Mental function= No difference seen
De Oliveira et al. (2012) Brazil	Outpatient n without VFs = 83 n with VFs = 43 mean age= 65.7 ± 6.3	Difference between groups not mentioned	QM	QUALEFFO	Physical function= No difference seen Mental function= No difference seen
Romagnoli et al. (2004) Italy	Primary care n without VFs = 93 n with VFs = 52 mean age= 63.7 ± 6.6	Difference between groups not mentioned	SQ	QUALEFFO	Physical function= 7.40 (2.50 to 12.29) Mental function= No difference seen
Alekna et al. (2006)	Osteoporosis centres n without VFs = 40	No difference in age and height	SQ	QUALEFFO	Physical function= No difference seen

Lithonia	n with VFs = 40 mean age= 67.4 ± 5.0				Mental function= No difference seen
Bianchi et al. (2005) Italy	Outpatient clinic n without VFs = 62 n with VFs = 38 mean age= 66.7 ± 8.6	Difference in age and femur BMD	SQ	QUALEFFO	Physical function= 18.90 (11.19 to 26.61) Mental function= No difference seen
Hakan Nur etal. (2012) Turkey	Outpatient clinic n without VFs = 99 n with VFs = 18 mean age= 60.7 ± 7.5	Difference in Age and duration of menopause	SQ	QUALEFFO	Physical function= 10.57 (0.61 to 20.53) Mental function= 11.68 (0.27 to 23.08)
Ramírez et al. (2008) Mexico	National Institute of Rehabilitation and the LAVOS study sample n without VFs = 80 n with VFs = 80 mean age= 72 ± 11.0	Difference in age	SQ	QUALEFFO SF36	Physical function= 13.03 (8.52 to 17.53) Mental function= 2.62 (0.59 to 4.60)
Yoh K et al. (2005) Japan	Outpatient clinic n without VFs = 19 n with VFs = 39 mean age= 73.07 ± 8.35	Difference between groups not mentioned	Japanese diagnostic criteria	SF-36 EQ-5D JOQOL	Physical function= No difference seen Mental function= No difference seen
Lombardi et al. (2004) Brazil	Outpatient Clinics n without VFs = 20 n with VFs = 15 mean age= 67.8 ± 5,3	No difference in age, height, or weight, and pain, but differ in kyphosis angle	QM	SF-36	Physical function= No difference seen Mental function= No difference seen
Grażyna et al. (2010) Poland	Outpatients n without VFs = 67 n with VFs = 18 mean age= 59.9 ± 5.2	Difference between groups not mentioned	SQ	QUALEFFO-41 WHOQOL-100	Physical function= No difference seen Mental function= No difference seen
DEMİRDAL et al. (2010) Turkey	Outpatients n without VFs = 30 n with VFs = 7 mean age= 67.8 ± 8.5	No difference in age, and in lumbar T score	Kleerek-oper's method	SF-36	Physical function= No difference seen Mental function= No difference seen
Case-control studies					
Tadic I et al. (2012) Serbia	Medical centres n without VFs = 50 n with VFs = 50 mean age= 67.4 ± 9.2	No difference in BMI, age of menopause, Education, but differ in age, Employment, and Marital status	SQ	QUALEFFO-41 EQ-5D	Physical function= 18.91 (10.86 to 26.95) Mental function= 9.70 (3.76 to 15.63)
Baseline data from a RCT					

Oleksik et al (2000) Across seven countries	Medical centres n without VFs = 302 n with VFs = 449 mean age= 67.75 ± 6.3	No difference in BMI, smoking, and family history of osteoporosis, but differ in age, Years postmenopause, and lumber BMD	SQ, BSQ and QM. At least two reading	NHP EQ-5D QUALEFFO	Physical function= 7.93 (5.87 to 9.98) Mental function= No difference seen

*A positive number indicates better QoL in those without vertebral fracture. Numbers are only given if there was statistical evidence of a difference reported between cases and controls

<u>Abbreviations</u>: BMD: bone mass density, BMI: bone mass index, EQ-5D: European Quality of Life-5 Dimensions, JOQOL: Japanese Osteoporosis Quality of Life Questionnaire, OQLQ: Osteoporosis Quality of Life Questionnaire, QM: Quantitative morphometry, QUALEFFO: Quality of life questionnaire of the European Foundation for Osteoporosis, SF-12: short form-12, SF-36: short form-36, SQ: semi-quantitative method, WHOQOL: World Health Organization Quality of Life Instruments, NHP: Nottingham Health Profile.

REFERENCE

1. *Klotzbuecher, C. M., Ross, P. D., Landsman, P. B., Abbott, T. A. and Berger, M. (2000), Patients with Prior Fractures Have an Increased Risk of Future Fractures: A Summary of the Literature and Statistical Synthesis. J Bone Miner Res, 15: 721–739. doi: 10.1359/jbmr.2000.15.4.721.*
2. Silverman, S.L., et al., *Prevalence of depressive symptoms in postmenopausal women with low bone mineral density and/or prevalent vertebral fracture: results from the Multiple Outcomes of Raloxifene Evaluation (MORE) study.* J Rheumatol, 2007. **34**(1): p. 140-4.
3. *Falling Short: Delivering Integrated Falls and Osteoporosis Services in England. All Party Parliamentary Osteoporosis Group, December 2004 https://www.nos.org.uk/document.doc?id=752. Access 27 February 2016.*
4. *Ferrans CE. Definitions and conceptual models of quality of life. In: Lipscomb J, Gotay CC, Snyder C, editors. Outcomes assessment in cancer. Cambridge, England: Cambridge University; 2005. p. 14–30.*
5. Ware, J.E., Jr., M. Kosinski, and S.D. Keller, *A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity.* Medical Care, 1996. **34**(3): p. 220-233.
6. EuroQol, G., *EuroQol - a new facility for the measurement of health-related quality of life.* Health Policy, 1990. **16**: p. 199-208.
7. Lips, P., Cooper, C., Agnusdei, D., Caulin, F., Egger, P., Johnell, O., Kanis, J. A., Kellingray, S., Leplege, A., Liberman, U. A., McCloskey, E., Minne, H., Reeve, J., Reginster, J. Y., Scholz, M., Todd, C., de Vernejoul, M. C., Wiklund, I., *Quality of life in patients with vertebral fractures: validation of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Working Party for Quality of Life of the European Foundation for Osteoporosis.* Osteoporos Int, 1999. **10**(2): p. 150-60.
8. Wilson, S., C.A. Sharp, and M.W. Davie, *Health-related quality of life in patients with osteoporosis in the absence of vertebral fracture: a systematic review.* Osteoporos Int, 2012. **23**(12): p. 2749-68.
9. *The Cochrane Collaboration Additional module 1: meta-analysis of continuous data. http://www.ibrarian.net/navon/paper/Additional_Module_1__Meta_analysis_of_continuous_.pdf?paperid=19001124. Access 27 February 2016.*
10. Hozo, S.P., B. Djulbegovic, and I. Hozo, *Estimating the mean and variance from the median, range, and the size of a sample.* BMC Med Res Methodol, 2005. **5**: p. 13.
11. *Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Erlbaum; 1988.*
12. Higgins Julian P T, T.S.G., Deeks Jonathan J, Altman Douglas G, *Measuring inconsistency in meta-analyses.* BMJ, 2003. **327**(7414): p. 557-560.
13. Salaffi. F., C.M.A., Malavolta. N., Carotti. M., Di Matteo. L., Scendoni. P., Grassi. W., *The burden of prevalent fractures on health-related quality of life in postmenopausal women with osteoporosis: the IMOF study.* J Rheumatol, 2007. **34**(7): p. 1551-60.
14. Lombardi, I., Jr.; Oliveira, L. M.; Monteiro, C. R.; Confessor, Y. Q.; Barros, T. L.; Natour, J., *Evaluation of physical capacity and quality of life in osteoporotic women.* Osteoporos Int, 2004. **15**(1): p. 80-5.
15. Yilmaz. F., S.F., Ergoz. E., Deniz. E., Ercalik. C., Yucel. S. D., Kuran. B., *Quality of life assessments with SF 36 in different musculoskeletal diseases.* Clin Rheumatol, 2008. **27**(3): p. 327-32.
16. Sanfelix-Genoves. J., H.I., Sanfelix-Gimeno. G., Reig-Molla. B., Peiro. S., *Impact of osteoporosis and vertebral fractures on quality-of-life. a population-based study in Valencia, Spain (The FRAVO Study).* Health Qual Life Outcomes, 2011. **9**: p. 20.

17. Fechtenbaum. J., C.C., Kolta. S., Horlait. S., Orcel. P., Roux. C., *The severity of vertebral fractures and health-related quality of life in osteoporotic postmenopausal women.* Osteoporos Int, 2005. **16**(12): p. 2175-9.
18. Oleksik. A., L.P., Dawson. A., Minshall. M. E., Shen. W., Cooper. C., Kanis. J., *Health-related quality of life in postmenopausal women with low BMD with or without prevalent vertebral fractures.* J Bone Miner Res, 2000. **15**(7): p. 1384-92.
19. de Oliveira Ferreira. N., d.S.R.B., Arthuso. M., Pinto-Neto. A. M., Caserta. N., Costa-Paiva. L., *Prevalence of vertebral fractures and quality of life in a sample of postmenopausal Brazilian women with osteoporosis.* Arch Osteoporos, 2012. **7**: p. 101-6.
20. Romagnoli. E., C.V., Nofroni. I., D'Erasmo. E., Paglia. F., De Geronimo. S., Pepe. J., Raejntroph. N., Maranghi. M., Minisola. S., *Quality of life in ambulatory postmenopausal women: the impact of reduced bone mineral density and subclinical vertebral fractures.* Osteoporos Int, 2004. **15**(12): p. 975-80.
21. Tadic. I., V.S.N., Tasic. L., Stevanovic. D., Dimic. A., Stamenkovic. B., Stojanovic. S., Milenkovic. S., *Validation of the osteoporosis quality of life questionnaire QUALEFFO-41 for the Serbian population.* Health Qual Life Outcomes, 2012. **10**: p. 74.
22. Alekna. V., T.M., Butenaite. V., *[The impact of subclinical vertebral fractures on health-related quality of life in women with osteoporosis].* Medicina (Kaunas), 2006. **42**(9): p. 744-50.
23. *Bianchi ML, Orsini MR, Saraifoger S, Ortolani S, Radaelli G, Betti S. Quality of life in post-menopausal osteoporosis. Health and Quality of Life Outcomes. 2005;3:78. doi:10.1186/1477-7525-3-78.*
24. Baczyk. G., O.T., Kleka. P., *Quality of life in postmenopausal women with reduced bone mineral density: psychometric evaluation of the Polish version of QUALEFFO-41.* Arch Med Sci, 2011. **7**(3): p. 476-85.
25. *Hakan Nur, N. Füsun Toraman., Postmenopozal Osteoporozda Vertebral Kırıkların Yaşam Kalitesine Etkisi. Turkish Journal of Osteoporosis 2012. 2011; 17.*
26. Yoh. K., T.K., Ishikawa. A., Ishibashi. T., Uchino. Y., Sato. Y., Tobinaga. M., Hasegawa. N., Kamae. S., Yoshizawa. M., *Health-related quality of life (HRQOL) in Japanese osteoporotic patients and its improvement by elcatonin treatment.* J Bone Miner Metab, 2005. **23**(2): p. 167-73.
27. Ramirez Perez. E., C.P., Wacher. N. H., Cardiel. M. H., del Pilar Diez Garcia. M., *Cultural adaptation and validation of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) in a Mexican population.* Clin Rheumatol, 2008. **27**(2): p. 151-61.
28. Demirdal, Ü.S., et al., *The relationship between vertebral fraktures and qulity of life in patients with osteoporosis.* Med Med J, 2010. **25**(1): p. 20-24.
29. Lezak M, H.D., Bigler E, Tranel D. Neuropsychological Assessment. 5. New York: Oxford University Press; 2012.