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ORIGINAL RESEARCH

Evaluating Health Related Quality of Life in Older People at Risk of Osteoporotic Fracture: A Head-to-Head Comparison of the EQ-5D-5L and AQoL-6D

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Abstract

We aimed to conduct a head-to-head comparison of the five-level version of the EuroQol five-dimensional questionnaire (EQ-5D-5L) and the Assessment of Quality of Life-6D (AQoL-6D) in measuring health-related quality of life (HRQoL) of older people at risk of osteoporotic fracture. Participants (n = 291) were recruited from the Third Affiliated Hospital of Sun Yat-Sen University. Study participants were asked to complete the EQ-5D-5L and the AQoL-6D and the results were converted to health-state utilities (HSUs) using population-specific scoring algorithms. The agreement among HSUs was evaluated using the intraclass correlation coefficient and illustrated using Bland–Altman plots. The minimally important difference (MID) for the EQ-5D and AQoL was set at 0.074 and 0.06. Information on socio-demographic background, socio-economic status and clinical risk factors in FRAX® was collected. Nonparametric statistics were used to explore the known-group validity measured by fracture risk. Mean (median) EQ-5D-5L and AQoL-6D HSUs were 0.73(0.83) and 0.74(0.79) for the study population. The EQ-5D-5L and the AQoL-6D HSUs strongly agreed and the HSU difference reached the MID level in both instruments. While a decreasing trend of AQoL-6D utilities was observed with worsening bone mineral density, EQ-5D-5L HSUs were similar in individuals with normal and osteopenic bone mineral densities. The AQoL-6D was also effective for measuring difference in independent living, relationships, mental health, coping and pain. Both instruments showed good known-group validity. The EQ-5D-5L and AQoL-6D are all valid measures for older people at risk of osteoporotic fracture.

Keywords Health-related quality-of-life · EQ-5D · Assessment of quality of life · Chinese · Osteoporosis

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1 Introduction

Osteoporosis is a systemic skeleton disorder characterized by low bone density and structural deterioration of bone tissue with an increased risk of fracture (Osteoporosis prevention, diagnosis, and therapy 2001). The prevalence of osteoporosis has risen in the past decade and now affects more than 30% of Chinese aged 50 years and older (Chen et al. 2016a, b). Osteoporosis has become a major health issue and incurs tremendous economic and disease burdens on Chinese society (Si et al. 2015). More importantly, patients with osteoporosis suffer decreased physical function, social function and well-being and increased pain. These health aspects are often addressed and measured by health-related quality of life (HRQoL) questionnaires. In addition, fracture assessment tools such as FRAX and the Garvan Bone Fracture Risk Calculator capture these health domains that potentially affect patients' HRQoL such as age, history of fracture, history of fall and so on (Kanis et al. 2017). It is important to evaluate the difference in HRQoL in patients at different levels of fracture risk.

There are several osteoporosis-specific HRQoL questionnaires including the Quality-of-Life Questionnaire of the European Foundation for Osteoporosis (Lips et al. 1997), the Osteoporosis Quality-of-Life Questionnaire (Cook et al. 1993) and the Osteoporosis-Targeted Quality-of-Life Questionnaire (Lydick et al. 1996). These questionnaires were developed to measure important physical and mental health domains specifically for osteoporosis. Additionally, generic multi-attribute utility instruments (MAUIs) are also commonly used in osteoporosis research, such as the EuroQol five-dimensional questionnaire (EQ-5D) (Lloyd and Pickard 2019), the Short Form 36 health survey questionnaire (Brazier et al. 1992) and the Assessment Quality of Life (AQoL) (Hawthorne et al. 1999).

Evaluation of HRQoL in osteoporosis-related clinical trials requires both disease-specific and general HRQoL instruments (Lips and van Schoor 2005). While disease-specific HRQoL instruments provide a greater degree of specificity, patients may struggle to complete the questionnaire (Aaronson 1989) and patients' HRQoL as evaluated by different disease-specific instruments cannot be directly compared (Fitzpatrick et al. 1992). Conversely, generic HRQoL instruments permit comparisons between different studies, disease areas and populations and synthesis of results across different studies, which is useful in meta-analysis (Yang et al. 2016). Additionally, health preference scores are available in some commonly-used generic HRQoL instruments (Drummond et al. 2015). By mapping the categorical measures in generic HRQoL instrument to a 0–1 (death—perfect health) preference score, HRQoL results from different studies or even different diseases can be compared.

Apart from their use in clinical trials, generic HRQoL instruments are also commonly used in observational osteoporosis research (Si et al. 2014b). For example, the International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS), the largest prospective observational osteoporosis study, included patients from 11 countries and used the EQ-5D to evaluate HRQoL after osteoporotic fractures (Svedbom et al. 2018). EQ-5D is easy to implement and it is the preferred measure of HRQoL in adults of the National Institute for Health and Care Excellence when they make funding recommendations (Longworth and Rowen 2013). However, it only measures small changes in HRQoL and has considerable ceiling effects, described as the proportion of "no problem" response in each health dimension (Selivanova et al. 2018; Campbell et al. 2016; Janssen et al. 2013). Although EQ-5D is the most dominant instrument in osteoporosis HRQoL studies (Si et al. 2014b), evidence comparing its performance with other generic preference-based HRQoL instruments is limited. Our study aimed to fill this research gap with a head-to-head comparison of the EQ-5D and AQoL to evaluate their performances in measuring HRQoL of patients at risk of osteoporotic fracture.

2 Method

2.1 Study Participants

Study participants were recruited from the Department of Rheumatology of the Third Affiliated Hospital of Sun Yat-Sen University between July 2017 and June 2018. Patients were included in the study if: (1) they were at risk of osteoporotic fracture assessed by a clinician; (2) they were 18 years or older at the time of survey; and (3) they were willing to participate in this study. All participants provided written informed consent before the survey. The study was approved by the Sun Yat-Sen University Ethics Committee.

2.2 HRQoL Instruments

The EQ-5D was developed by the EuroQol Group. It has two versions to measure HRQoL in adults: five-dimensional three-level (EQ-5D-3L) and five-dimensional five-level (EQ-5D-5L) versions (Devlin and Brooks 2017). The EQ-5D-3L was introduced before the EQ-5D-5L, but they share the same five dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression (Devlin and Brooks 2017). The EQ-5D-3L has become the most widely-used MAUI globally (Chen et al. 2016a, b). However, concerns have arisen over the poor sensitivity and ceiling effects of the EQ-5D-3L. Therefore, the EQ-5D-5L was introduced in 2009. This comprises 3125 (5^5) health states and has a significantly reduced ceiling effect (Herdman et al. 2011; Devlin and Brooks 2017; Ferreira et al. 2016).

In this study, the Chinese version of EQ-5D-5L was employed and was scored using the Chinese-specific EQ-5D-5L value set (Luo et al. 2017). For the Chinese tariff, the EQ-5D-5L health-state utilities (HSUs) ranged from -0.39 (the worst health state according to the EQ-5D-5L classification system) to 1 (full health), whilst 0 represents death (Luo et al. 2017). Evidence has suggested that the mean minimally important difference (MID) for the EQ-5D is 0.074 (Walters and Brazier 2005). In addition to the EQ-5D-5L, a visual analogue scale (VAS) was also included in the EQ-5D questionnaire for participants to self-rate their health that day. The EQ-VAS was shown in the form of a vertical, hash-marked, 20-cm anchor ranging from 0 (worst imaginable health) to 100 (best imaginable health) (Whitehead and Ali 2010; Herdman et al. 2011). The EQ-VAS was rescaled to a 0–1 value for comparison.

The AQoL was introduced by the AQoL group in Australia in the late 1990s. Five different versions exist: AQoL-8D (35 items), AQoL-7D (26 items), AQoL-6D (20 items), AQoL-4D (12 items) and AQoL-8 (8 items). The AQoL is one of the most comprehensive MAUIs globally (Chen et al. 2016a, b). While more health domains are included, it also poses a potential time burden for participants to complete the questionnaire (Richardson et al. 2014). After compromising between the number of dimensions/items and the completion time, the AQoL-6D was considered most appropriate for this study. AQoL-6D is a validated instrument and its psychometric properties are important in evaluating osteoporosis-related HRQoL (Shen et al. 2014). It has six dimensions: independent living, relationships, mental health, coping, pain and senses. The Chinese version AQoL-6D was scored using its official tariff developed in Australia, which produces both overall utility score and six dimensions scores. The AQoL-6D can define a total of 6.58×10^{13} health states and its utilities range from -0.04 to 1. With the disvalues in each of the health dimensions in AQoL-6D, dimension effects were calculated for different levels of fracture risk measured by bone mineral density (BMD), risk of a major fracture and risk of a hip fracture. The MID for the AQoL was set at 0.06 (Hawthorne and Osborne 2005).

2.3 Data Collection

HRQoL data, socio-demographic and socio-economic characteristics and osteoporosis-related data were collected in the survey. Specifically, the following information was collected: age, sex, education level, family income, weight, height and self-reported diagnosis of osteoporosis. Living standard was measured by the per-adult household income, which was calculated by the annual household income divided by the number of adults in the household (Deaton 1997). Additionally, to evaluate whether EQ-5D-5L and AQoL-6D could be used to gauge the difference in HRQoL of patients with different fracture risk levels, BMD at the femoral neck (expressed as a T-score) and clinical risk factors (in FRAX®) were also collected (Kanis et al. 2008). BMD was measured by the dual-energy X-ray absorptiometry (DXA) using a Hologic Discovery A system at the vertebrae L2-L4, the femoral neck and the pelvis. In this study, we used the BMD at femoral neck to define whether the patient had normal BMD, osteopenic BMD or osteoporotic BMD (Kanis 2002). Osteoporotic BMD was defined as a BMD 2.5 standard deviation (SD) or more below the average value for premenopausal women which was provided by the Hologic Discovery A system (i.e. T score ≤ -2.5) (Kanis 2002). An osteopenic BMD was defined as a BMD between 1 and 2.5 SD below the average value for premenopausal women (i.e. $-2.5 <$ T score < -1) and a normal BMD was defined as a T-score ≥ -1 (Kanis 2002). HRQoL instruments were self-administered. Study participants completed the questionnaires themselves using paper and pencil.

2.4 Statistical Analysis

The agreements between the EQ-5D-5L and AQoL-6D HSUs were evaluated using intraclass correlation coefficients (ICCs). An ICC > 0.7 indicates a strong agreement (Fayers and Machin 2013). Additionally, Bland–Altman plots and the 95% limits of agreement were provided to visually quantify agreement between the two MAUIs (Bland and Altman 1986; Myles and Cui 2007). To calculate 10-year risks of major osteoporotic fracture and hip fracture, the FRAX calculator for the Chinese population (https://www.shef.ac.uk/FRAX) was used (Diseases). High risk groups were defined using cut-off 10-year risks of a major and hip fracture at 4% and 1.3%, respectively (Zhang et al. 2014). The Kruskal–Wallis test was used to measure correlations among three BMD groups (normal BMD, osteopenic BMD and osteoporotic BMD) and the Wilcoxon rank-sum test was used to measure the correlations among different fracture risk groups (McDonald 2009). To evaluate the sensitivity of HSU in detecting the difference between groups, effect size was reported using Cohen's *d*, with 0.41 regarded as the recommended minimum effect size, 1.15 as moderate and 2.70 as strong (Ferguson 2009). The Tobit model was used to further investigate the known-group validity when incorporating other covariates that were not listed in FRAX, such as having a fall, per-adult family income and school education level (Austin et al. 2000). We used three statistical models to test the known-group validity. Model 1 included individual risk factors in the FRAX; Models 2 and 3 included a composite 10-year risk of a major and hip osteoporotic fracture and other risk factors that are not included in FRAX. All statistical analyses were conducted using STATA MP 15.1 (StataCorp, College Station, TX, USA) and statistical significance was set as a *p*-value equal to or less than 0.05 (two-tailed).

3 Results

3.1 Characteristics of Study Participants

Two hundred ninety-one participants completed the questionnaire. The mean age was 63.4 years and 82% were women. Approximately 90% of the study participants had school education and one third had an income lower than the national average. The average T-score was −2.1 and around one fourth of patients had a previous fracture. Additionally, 224 (77%) and 202 (69.4%) patients were classified as high risk of having a major and hip fracture, respectively. More detailed participant characteristics are shown in Table 1.

Table 1 Characteristics of study participants

	N = 291
Number of women (%)	237 (82.0%)
Age, years (SD)	63.4 (10.1)
BMI, kg/m^2 (SD)	22.7 (3.7)
Education	
No school education	33 (11.6%)
Primary school	67 (23.3%)
Junior high school	71 (24.7%)
Senior high school or equivalent	78 (27.1%)
University education or above	39 (13.5%)
Household income per annum, RMB Yuan (SD)	51,479 (52,684)
*Number of patients with per adult household income lower than average income in China**	98 (33.7%)
Number of patients with previous fracture (%)	69 (24.9%)
Bone mineral density, T-score (SD)	− 2.1 (0.8)
Number of patients with osteoporosis** (%)	91 (31.3%)
Number of patients with high risk of having a major osteoporotic fracture (%)***	224 (77.0%)
Number of patients with high risk of having a hip osteoporotic fracture (%)***	202 (69.4%)

BMI, body mass index; SD, standard deviation,

*National average income per annum is set at 28,228 Yuan (China 2019)

**Diagnosis of osteoporosis is defined by a T-score equal to or lower than -2.5 (Osteoporosis prevention, diagnosis, and therapy 2001)

***High risk groups are defined using 10-year risk of having a major/hip fracture evaluated by FRAX. Cutoff 10-year risk is 4% and 1.3% for a major and hip osteoporotic fracture respectively (Zhang et al. 2014)

Table 2 Comparison of the EQ-5D-5L, the AQoL-6D and EQ-VAS

Measures	Theoretical range	Observed range	Mean (SD)	Median (5th, 95th percentile)	Ceiling effect (n)	Floor effect (n)
EQ-5D-5L	− 0.39–1.00	− 0.29–1.00	0.75 (0.26)	0.83 (0.16, 1.00)	33	0
AQoL-6D	− 0.04–1.00	0.16–1.00	0.74 (0.19)	0.79 (0.35, 0.98)	13	0
EQ-VAS	0–1	0–1	0.68 (0.17)	0.70 (0.40, 1.00)	13	1

EQ-5D-5L, the five-level version of the EuroQol five-dimensional questionnaire; AQoL-6D, the Assessment of Quality of Life—6D; VAS, visual analogue scale, SD, standard deviation

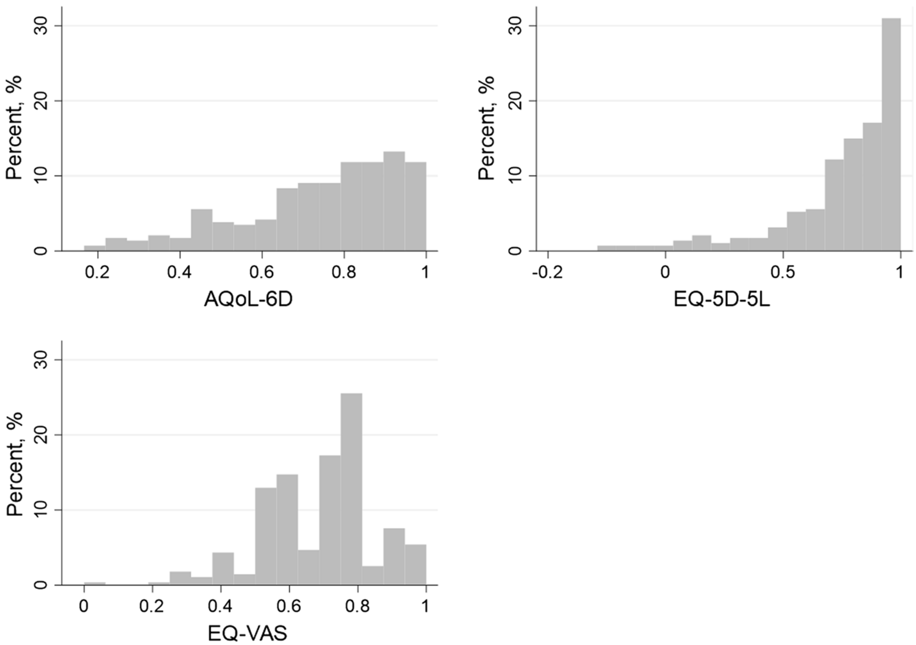

Fig. 1 Distribution of health state utilities (HSUs) by instrument. EQ-5D-5L, the five-level version of the EuroQol five-dimensional questionnaire; AQoL-6D, the Assessment of Quality of Life—6D. The distributions of EQ-5D-5L and AQoL-6D HSUs were all left-skewed and the EQ-VAS scores were bimodal

3.2 Descriptive EQ-5D-5L and AQoL-6D Statistics

The summary of the comparison of HSUs measured using EQ-5D-5L, AQoL-6D and EQ-VAS is given in Table 2. The mean (median) HSUs were 0.75 (0.83), 0.74 (0.79), and 0.68 (0.70) for EQ-5D-5L, AQoL-6D and EQ-VAS, respectively. The distributions of EQ-5D-5L and AQoL-6D HSUs were all left-skewed and the EQ-VAS scores were bimodal (Fig. 1). According to EQ-5D-5L and AQoL-6D classification systems, 33 (11%) and 13 (4%) participants reported no problem in all health dimensions, and the EQ-VAS measured 13 (4%) participants as having the best imaginable health. No participant reported the worst response level in all health dimensions in EQ-5D-5L and AQoL-6D. The observed worst HSUs were -0.29 and 0.16 for EQ-5D-5L and AQoL-6D, respectively, and one participant scored the worst imaginable health in the EQ-VAS.

3.3 Agreement Between EQ-5D-5L and AQoL-6D

EQ-5D-5L and AQoL-6D HSUs strongly agreed in our study population, with an ICC of 0.75 (95% confidence interval, CI: 0.70, 0.80). Bland–Altman plots (Fig. 2) further illustrated the agreement between HSUs and the 95% limit of agreement (-0.33, 0.30) contained 95% of the different scores.

3.4 Known-Group Validity and Sensitivity of EQ-5D-5L and AQoL-6D

Mean HSUs measured by EQ-5D-5L, AQoL-6D and EQ-VAS in different BMD and fracture risk groups are presented in Table 3. Between-group variations of EQ-5D-5L and AQoL-6D HSUs were all statistically significant in different BMD and fracture risk groups. Conversely, the between-group variation of EQ-VAS HSUs was not statistically significant.

HSUs were similar in study participants with normal and osteopenic BMDs when they were evaluated using EQ-5D-5L or EQ-VAS. When the AQoL-6D was used, there was a consistent decrease in HSUs moving from normal BMD to the lower BMD levels. The EQ-5D-5L and AQoL-6D HSUs were 0.10 (95% CI 0.03, 0.17) and 0.07 (95% CI 0.02, 0.13) higher in the low risk group than in the high risk group when measured by the 10-year risk of a major fracture. When study participants were divided by the 10-year risk of hip fracture, the difference in EQ-5D-5L and AQoL-6D HSUs was 0.11 (95% CI 0.05, 0.17) and

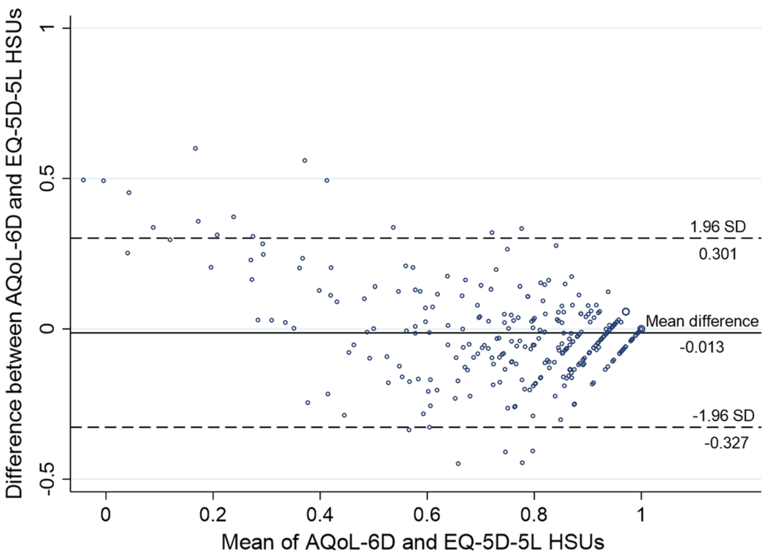

Fig. 2 Bland–Altman plots of comparison among EQ-5D-5L and AQoL-6D health state utilities (HSUs). EQ-5D-5L, the five-level version of the EuroQol five-dimensional questionnaire; AQoL-6D, the Assessment of Quality of Life—6D. The mean difference of the EQ-5D-5L and AQoL-6D HSUs is -0.013. Moreover, the 95% limit of agreement (– 0.327, 0.301) contained 95% of the different scores

Table 3 Known-group validity of the EQ-5D-5L, the AQoL-6D health state utilities (HSUs) and EQ-VAS by bone mineral density (BMD) and 10-year fracture risk

	EQ-5D-5L (95% CI)	p value	AQoL-6D (95% CI)	p value	EQ-VAS* (95% CI)	p value
BMD **		$p=0.01$		$p=0.001$		$p=0.18$
T-score ≤ −2.5	0.69 (0.63, 0.75)		0.70 (0.65, 0.74)		0.66 (0.63, 0.70)	
− 2.5 < T-score < -1.0	0.78 (0.74, 0.82)		0.74 (0.71, 0.77)		0.70 (0.66, 0.73)	
T-score > -1.0	0.79 (0.73, 0.85)		0.80 (0.76, 0.84)		0.70 (0.66, 0.74)	
10-year risk of a major osteoporotic fracture ***		$p<0.001$		$p=0.001$		$p=0.06$
≥4%	0.73 (0.70, 0.77)		0.72 (0.70, 0.75)		0.67 (0.65, 0.70)	
<4%	0.83 (0.77, 0.89)		0.80 (0.75, 0.84)		0.72 (0.68, 0.76)	
Mean difference	0.10 (0.03, 0.17)		0.07 (0.02, 0.13)		0.05 (− 0.001, 0.10)	
Effect size	0.39 (0.11, 0.66)		0.38 (0.10, 0.65)		0.28 (− 0.001, 0.56)	
10-year risk of a hip osteoporotic fracture ***		$p<0.001$		$p=0.007$		$p=0.052$
≥1.3%	0.72 (0.68, 0.76)		0.72 (0.69, 0.75)		0.67 (0.64, 0.69)	
<1.3%	0.83 (0.79, 0.87)		0.79 (0.76, 0.83)		0.72 (0.69, 0.76)	
Mean difference	0.11 (0.05, 0.17)		0.07 (0.03, 0.12)		0.05 (0.01, 0.10)	
Effect size	0.43 (0.18, 0.68)		0.39 (0.14, 0.64)		0.32 (0.06, 0.58)	

EQ-5D-5L, the five-level version of the EuroQol five-dimensional questionnaire; AQoL-6D, the Assessment of Quality of Life—6D scale; VAS, visual analogue scale

*VAS is evaluated on a thermometer from 0 (worst imaginable health state) to 100 (best imaginable health state). The rating on the VAS is converted to a score from 0 to 1

**Between-group variation is evaluated using the Kruskal–Wallis test

***Between-group variation is evaluated using the Wilcoxon rank-sum test

0.07 (95% CI 0.03, 0.12), respectively. All of the differences in HSU by BMD level and fracture risk reached the MID for each MAUI.

Regarding the sensitivity of the instruments, neither of the effect sizes reached the minimum effect size when the risk of population was defined by 10-year risk of a major fracture. Conversely, the effect size of the difference in EQ-5D-5L HSUs was 0.43, which did reach the minimum effect size level (Table 3).

Further known-group validity analyses of EQ-5D-5L and AQoL-6D using regression analyses are shown in Table 4. The EQ-5D-5L and AQoL-6D both detected significant HSU differences between patients with different levels of 10-year risk of major and hip fractures. Moreover, the magnitude of differences in EQ-5D-5L and AQoL-6D HSU were similar. As individual covariates (Model 1), rheumatoid arthritis, osteoporotic BMD and a lower school education were associated with significantly lower EQ-5D-5L HSUs. Secondary osteoporosis was an additional factor of lower AQoL-6D HSUs with all EQ-5D-5L HSU influencing factors. Of all risk factors that were included in FRAX (models 2 and 3), high 10-year risks of major and hip fracture and lower school education were significantly associated with lower EQ-5D-5L and AQoL-6D HSUs.

3.5 What HRQoL Dimensions were Affected by Increasing Fracture Risk?

The effects of fracture risks measured by BMD and 10-year risks of major fracture and hip fracture on each of the six AQoL-6D dimensions are presented in Fig. 3. As can be seen in Fig. 3a, b, patients with higher fracture risk (regardless whether major or hip) had lower scores in five HRQoL domains: independent living, relationships, mental health, coping and pain than participants with lower fracture risks.

Similarly, sense dimension scores were similar among participants with different BMD levels (Fig. 3c). There were proportionate decreases of HRQoL scores regarding relationships and mental health for patients with osteoporotic and osteopenic BMDs compared with their normal BMD counterparts. HRQoL scores of independent living were similar in study participants with normal and osteopenic BMDs. Patients with osteoporotic BMDs had an approximately 20% reduction in their HRQoL scores of independent living compared with those with normal BMDs. Additionally, HRQoL coping and pain scores were similar between participants with osteopenic and osteoporotic BMDs and all were lower than those of participants with normal BMDs.

The effects of fracture risks measured by BMD and 10-year risks of major fracture and hip fracture on each of the five EQ-5D-5L dimensions are presented in Table 5. There were higher proportion of study participants who had lower fracture risk or higher BMD level reported “no problems” in each of the EQ-5D-5L dimensions. However, there was no clear trend in distribution of reporting problems from “slight problems” to “extreme problems” in the EQ-5D-5L health dimensions.

4 Discussion

Selecting a preference-based HRQoL instrument is important for observational research and clinical trials in the field of osteoporosis. This study reports the performance of a head-to-head comparison between the EQ-5D-5L and the AQoL-6D for measuring HSUs of people at risk of osteoporotic fracture. EQ-5D-5L and AQoL-6D HSUs strongly agree. The HSU differences by BMD and fracture risks reach the MID level in both instruments which

Table 4 Known-group validity of the EQ-5D-5L and the AQoL-6D health state utilities (HSUs) by clinical risk factors

Risk factors	EQ-5D-5L			AQoL-6D		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
10-year risk of a major osteoporotic fracture (high risk)		**– 0.09**			**– 0.08**	
10-year risk of a hip osteoporotic fracture (high risk)			**– 0.07**			**– 0.05**
Risk factors included in FRAX						
Age (≥ 60 years)	– 0.04			0.01		
Sex: women	– 0.03			-0.02		
BMI: overweight/obese	0.00			0.01		
Previous fracture	– 0.01			0.00		
Parent fracture hip	0.14			0.11		
Current smoking	0.04			0.01		
Glucocorticoids	0.01			– 0.00		
Rheumatoid arthritis	**– 0.13**			**– 0.10**		
Secondary osteoporosis	– 0.07			**– 0.09**		
Alcohol 3 or more units per day	– 0.01			– 0.06		
BMD: osteoporosis	**– 0.07**			**– 0.05**		
Risk factors not included in FRAX						
Fall	– 0.04	– 0.05	– 0.03	– 0.03	– 0.05	– 0.03
Per-adult household income (higher than national average)	0.03	0.03	0.05	0.04	0.03	0.04
Education	**0.05**	**0.05**	**0.02**	**0.02**	**0.05**	**0.02**

EQ-5D-5L, the five-level version of the EuroQol five-dimensional questionnaire; AQoL-6D, the Assessment of Quality of Life—6D; BMD, bone mineral density

Coefficients in bold denote statistical significance

Model 1 includes individual risk factors; Models 2 and 3 include 10-year risk of a major and hip osteoporotic fracture and other risk factors that are not included in FRAX

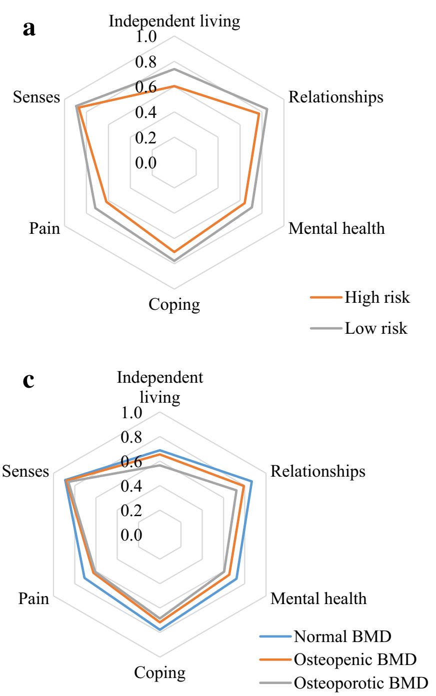

Fig. 3 Health-related quality of life (HRQoL) scores by the Assessment of Quality of Life—6D (AQoL-6D) dimension, bone mineral density (BMD) level and FRAX 10-year fracture risk. **a** HRQoL scores by 10-year risk of a major osteoporotic fracture; **b** HRQoL score by 10-year risk of a hip osteoporotic fracture; **c** HRQoL score by BMD level. Patients with higher fracture risk (regardless whether major or hip) or osteoporotic BMD have lower HRQoL scores in five HRQoL domains: independent living, relationships, mental health, coping and pain than participants with lower fracture risks. HRQoL score of sense does not change in different levels of fracture risk or BMD

suggests they are valid HRQoL measures in this population. The AQoL-6D has also shown its usefulness for gauging changes of HRQoL in independent living, relationships, mental health, coping and pain. Conversely, EQ-VAS does not differentiate between individuals with different levels of fracture risk and BMDs.

The literature to date has focused on reporting HRQoL of patients who have a fracture event (Silverman 2005). The landmark ICUROS study systematically reported HSUs 4, 12 and 18 months after hip, vertebral and distal forearm fracture in 11 countries (Svedbom et al. 2018). While the EQ-5D HSUs reported in ICUROS provide invaluable data for health economic evaluation of secondary fracture prevention, HSUs of patients at risk of but without a fracture largely remain unknown. Our study has shown that HRQoL decreased in patients with high fracture risks. This HRQoL decrease should be noted by the care givers, clinicians, health care researchers and health economists when conducting economic evaluation of primary fracture preventions.

Measuring HRQoL covers a broad range of health domains including physical, mental, emotional and social functioning. While physical function is included in most osteoporosis-specific HRQoL questionnaires (Madureira et al. 2012), social interaction and coping were overlooked in many of these and generic HRQoL instruments such as EQ-5D. Physical function decreases following a fracture and the dysfunction persists for around

Table 5 EQ-5D-5L profile of study participants by bone mineral density (BMD) and 10-year fracture risk

	10-year risk of a major osteoporotic fracture		10-year risk of a hip osteoporotic fracture		BMD level		
	Low risk	High risk	Low risk	High risk	Normal BMD	Osteo-penic BMD	Osteo-porotic BMD
Mobility (%)							
No problems	68.7	45.5	61.8	46.0	58.2	55.4	38.5
Slight problems	23.9	29.9	28.1	28.7	24.1	29.8	30.8
Moderate problems	4.5	15.2	7.9	14.9	13.9	8.3	17.6
Severe problems	0.0	7.1	0.0	7.9	1.3	5.8	8.8
Unable to walk about	3.0	2.2	2.3	2.5	2.5	0.8	4.4
Self-care (%)							
No problems	88.1	68.8	83.2	68.8	78.5	78.5	61.5
Slight problems	7.5	21.9	13.5	20.8	16.5	17.4	22.0
Moderate problems	0.0	4.0	1.1	4.0	0.0	2.5	6.6
Severe problems	1.5	3.1	1.1	3.5	3.8	0.0	5.5
Unable to walk about	3.0	2.2	1.1	3.0	1.3	1.7	4.4
Usual activities (%)							
No problems	82.1	55.4	75.3	55.5	68.4	65.3	50.6
Slight problems	11.9	25.0	16.9	24.3	21.5	23.1	20.9
Moderate problems	0.0	11.6	4.5	10.9	2.5	7.4	16.5
Severe problems	3.0	4.9	2.3	5.5	6.3	1.7	6.6
Unable to walk about	3.0	3.1	1.1	4.0	1.3	2.5	5.5
Pain/discomfort (%)							
No problems	28.4	22.3	25.8	22.8	26.6	18.2	28.6
Slight problems	55.2	42.4	59.6	39.1	49.4	50.4	35.2
Moderate problems	13.4	28.6	12.4	30.7	17.7	25.6	30.8
Severe problems	3.0	4.0	2.3	4.5	3.8	4.1	3.3
Unable to walk about	0.0	2.7	0.0	3.0	2.5	1.7	2.2
Anxiety/depression (%)							
No problems	50.8	41.4	50.6	40.5	55.8	39.2	38.9
Slight problems	27.7	40.1	32.2	39.5	26.0	43.3	38.9
Moderate problems	16.9	15.3	13.8	16.5	14.3	14.2	18.9
Severe problems	4.6	2.7	3.5	3.0	3.9	2.5	3.3
Unable to walk about	0.0	0.5	0.0	0.5	0.0	0.8	0.0

EQ-5D-5L, the five-level version of the EuroQol five-dimensional questionnaire

20 years after fracture (Johansson et al. 2019). However, disutility in physical function was not significantly different based on BMD alone (Martin et al. 2002). When measuring HRQoL of individuals with reduced BMDs and no prior fracture, HRQoL in domains such as mental function, social interaction and coping becomes important. Social interaction and coping ability decreased in individuals diagnosed with osteoporosis because of their fear of falling or future fracture, depression, altered body image and many other factors (Kerr et al. 2017). This study has shown that AQoL-6D was effective for detecting

decreased HRQoL in independent living, relationships, mental health, coping and pain in individuals with different levels of fracture risks and BMDs. Moreover, the AQoL-6D scoring algorithm could be used to quantify decreases in each health domain. Vision, hearing and speaking are covered in the sense domain in the AQoL-6D. However, they are less related to bone health. Not surprisingly, there was no difference in HRQoL score in the sense dimension among participants with different levels of fracture risk and BMDs.

The general agreement of EQ-5D-5L and AQoL-6D HSUs was strong among our study participants. The mean EQ-5D-5L and AQoL-6D HSUs were similar in participants with high 10-year fracture risk and people with normal and osteoporotic BMDs (Table 2). However, divergence in HSUs measured by these two instruments existed in participants with low 10-year fracture risk and with osteopenic BMDs. This might be because the AQoL-6D measures more health domains than the EQ-5D. Decreased HRQoL was observed in five of the six domains in the AQoL-6D in people with osteopenic BMD compared with their counterparts with normal BMDs (Fig. 3). Of note, the decrease in the "pain" domain was more profound when transiting from normal to osteopenic BMD than that from osteopenic to osteoporotic BMD. This finding raised the importance of managing people with osteopenia to reduce the burden of fracture as over half of the fragility fractures occurred in the population with osteopenic BMDs (Pasco et al. 2006).

Using FRAX to assess individual fracture risk is clinically effective in managing people at risk of osteoporotic fractures (Kanis et al. 2008). With recommended cut-off 10-year probability of major osteoporotic fracture and hip fracture, clinicians can target those who need intervention to prevent future fracture. The recommended intervention thresholds based on 10-year probabilities of major osteoporotic fracture and hip fracture were 4.0% and 1.3% in the Chinese population (Zhang et al. 2014). Our study results indicated that these cut-off values also distinguished the population groups accordingly to their HRQoL. Based on the 10-year risk of major osteoporotic fracture, high risk individuals had lower EQ-5D-5L and AQoL-6D HSUs of 0.09 and 0.08, respectively, compared with those at low risk. Both HSU differences were higher than the MIDs (Hawthorne and Osborne 2005; Walters and Brazier 2005).

This study has several limitations. First, the study participants were recruited in a tertiary hospital in China. Therefore the study results might not be generalizable to other populations. Second, given the known ceiling effects from the EQ-5D-3L (Devlin and Brooks 2017), this study compared the EQ-5D-5L with the AQoL-6D. Comparisons between the EQ-5D-3L and the AQoL-6D cannot be made. Third, the scoring algorithms for the EQ-5D-5L and the AQoL-6D were derived from two different populations. The differences in HSUs might be influenced to the difference in health preference in the original survey population. Future studies to generate AQoL-6D preference weights in the Chinese population are encouraged. Fourth, we only included 291 participants in the study, which may have an impact when assessing the sensitivity of HSUs in detecting the difference between groups. In addition, we did not collect the site of previous fracture. The previous fracture might have a statistically significant impact on HRQoL if they occurred at the hip or vertebrae, but at other sites it is possible that fractures might indeed have only had trivial impacts (Si et al. 2014a). Lastly, this study only measured cross-sectional HRQoL, it will be useful to evaluate whether the EQ-5D-5L and AQoL-6D are able to gauge the HRQoL change along with the longitudinal change in fracture risk.

In summary, the study reported a head-to-head comparison of EQ-5D-5L and AQoL-6D for measuring HRQoL of individuals at risk of osteoporotic fracture. The agreement of HSUs derived from these two instruments was strong and the difference in HSUs by fracture risk all reached the MID. Therefore both instruments are valid when HSU is a major outcome in an observational study or clinical trial on osteoporosis.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by LS, LT, GC, XZ, JL, QL and ZL. The first draft of the manuscript was written by LS and LT. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with Ethical Standards

Conflicts of interest LS, LT, YX, GC, MH, MY, YZ, XZ, YJ, QW, JG and AJP declare no conflicts of interest.

Availability of Data and Materials The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

References

Aaronson, N. K. (1989). Quality of life assessment in clinical trials: Methodologic issues. *Controlled Clinical Trials, 10*(4(Supplement 1)), 195–208. https://doi.org/10.1016/0197-2456(89)90058-5.

Austin, P. C., Escobar, M., & Kopec, J. A. (2000). The use of the Tobit model for analyzing measures of health status. *Quality of Life Research, 9*(8), 901–910. https://doi.org/10.1023/A:1008938326604.

Bland, J. M., & Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet, 1*(8476), 307–310.

Brazier, J. E., Harper, R., Jones, N. M., O'Cathain, A., Thomas, K. J., Usherwood, T., et al. (1992). Validating the SF-36 health survey questionnaire: New outcome measure for primary care. *BMJ, 305*(6846), 160–164. https://doi.org/10.1136/bmj.305.6846.160.

Campbell, J. A., Palmer, A. J., Venn, A., Sharman, M., Otahal, P., & Neil, A. (2016). A head-to-head comparison of the EQ-5D-5L and AQoL-8D multi-attribute utility instruments in patients who have previously undergone bariatric surgery. *Patient, 9*(4), 311–322. https://doi.org/10.1007/s40271-015-0157-5.

Chen, G., Khan, M. A., Iezzi, A., Ratcliffe, J., & Richardson, J. (2016a). Mapping between 6 multiattribute utility instruments. *Medical Decision Making, 36*(2), 160–175. https://doi.org/10.1177/0272989x15578127.

Chen, P., Li, Z., & Hu, Y. (2016b). Prevalence of osteoporosis in China: A meta-analysis and systematic review. *BMC Public Health, 16*(1), 1039. https://doi.org/10.1186/s12889-016-3712-7.

China, N. B. O. S. O. (2019). *Income and expenditure*https://www.stats.gov.cn/tjsj/zxfb/201901/t20190121_1645791.html2019.

Cook, D. J., Guyatt, G. H., Adachi, J. D., Clifton, J., Griffith, L. E., Epstein, R. S., et al. (1993). Quality of life issues in women with vertebral fractures due to osteoporosis. *Arthritis and Rheumatism, 36*(6), 750–756. https://doi.org/10.1002/art.1780360603.

Deaton, A. (1997). *The analysis of household surveys: a microeconometric approach to development policy*: The World Bank.

Devlin, N. J., & Brooks, R. (2017). EQ-5D and the EuroQol group: Past, present and future. *Applied health Economics and Health Policy, 15*(2), 127–137. https://doi.org/10.1007/s40258-017-0310-5.

Diseases, C. F. M. B. FRAX calculation tool (China). https://www.sheffield.ac.uk/FRAX/tool.aspx?country=312019.

Drummond, M. F., Sculpher, M. J., Claxton, K., Stoddart, G. L., & Torrance, G. W. (2015). *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press.

Fayers, P. M., & Machin, D. (2013). *Quality of life: the assessment, analysis and interpretation of patient-reported outcomes*. Hoboken: Wiley.

Ferguson, C. J. (2009). An effect size primer: A guide for clinicians and researchers. *Professional Psychology: Research and Practice, 40*(5), 532.

Ferreira, L. N., Ferreira, P. L., Ribeiro, F. P., & Pereira, L. N. (2016). Comparing the performance of the EQ-5D-3L and the EQ-5D-5L in young Portuguese adults. *Health and Quality of Life Outcomes, 14*(1), 89. https://doi.org/10.1186/s12955-016-0491-x.

Fitzpatrick, R., Fletcher, A., Gore, S., Jones, D., Spiegelhalter, D., & Cox, D. (1992). Quality of life measures in health care I: Applications and issues in assessment. *BMJ, 305*(6861), 1074–1077. https://doi.org/10.1136/bmj.305.6861.1074.

Hawthorne, G., & Osborne, R. (2005). Population norms and meaningful differences for the Assessment of Quality of Life (AQoL) measure. *Australian and New Zealand Journal of Public Health, 29*(2), 136–142.

Hawthorne, G., Richardson, J., & Osborne, R. (1999). The Assessment of Quality of Life (AQoL) instrument: A psychometric measure of health-related quality of life. *Quality of Life Research, 8*(3), 209–224.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M., Kind, P., Parkin, D., et al. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research, 20*(10), 1727–1736. https://doi.org/10.1007/s11136-011-9903-x.

Janssen, M. F., Pickard, A. S., Golicki, D., Gudex, C., Niewada, M., Scalone, L., et al. (2013). Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: A multi-country study. *Quality of Life Research, 22*(7), 1717–1727. https://doi.org/10.1007/s11136-012-0322-4.

Johansson, L., Svensson, H. K., Karlsson, J., Olsson, L. E., Mellström, D., Lorentzon, M., et al. (2019). Decreased physical health-related quality of life—a persisting state for older women with clinical vertebral fracture. *Osteoporosis International*. https://doi.org/10.1007/s00198-019-05044-0.

Kanis, J. A. (2002). Diagnosis of osteoporosis and assessment of fracture risk. *Lancet, 359*(9321), 1929–1936. https://doi.org/10.1016/s0140-6736(02)08761-5.

Kanis, J. A., Harvey, N. C., Johansson, H., Odén, A., McCloskey, E. V., & Leslie, W. D. (2017). Overview of fracture prediction tools. *Journal of Clinical Densitometry: The Official Journal of the International Society for Clinical Densitometry, 20*(3), 444–450. https://doi.org/10.1016/j.jocd.2017.06.013.

Kanis, J. A., Johnell, O., Oden, A., Johansson, H., & McCloskey, E. (2008). FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporosis International, 19*(4), 385–397. https://doi.org/10.1007/s00198-007-0543-5.

Kerr, C., Bottomley, C., Shingler, S., Giangregorio, L., de Freitas, H. M., Patel, C., et al. (2017). The importance of physical function to people with osteoporosis. *Osteoporosis International, 28*(5), 1597–1607. https://doi.org/10.1007/s00198-017-3911-9.

Lips, P., Cooper, C., Agnusdei, D., Caulin, F., Egger, P., Johnell, O., et al. (1997). Quality of life as outcome in the treatment of osteoporosis: The development of a questionnaire for quality of life by the European Foundation for Osteoporosis. *Osteoporosis International, 7*(1), 36–38.

Lips, P., & van Schoor, N. M. (2005). Quality of life in patients with osteoporosis. *Osteoporosis International, 16*(5), 447–455. https://doi.org/10.1007/s00198-004-1762-7.

Lloyd, A., & Pickard, A. S. (2019). The EQ-5D and the EuroQol group. *Value in Health, 22*(1), 21–22. https://doi.org/10.1016/j.jval.2018.12.002.

Longworth, L., & Rowen, D. (2013). Mapping to obtain EQ-5D utility values for use in NICE health technology assessments. *Value Health, 16*(1), 202–210. https://doi.org/10.1016/j.jval.2012.10.010.

Luo, N., Liu, G., Li, M., Guan, H., Jin, X., & Rand-Hendriksen, K. (2017). Estimating an EQ-5D-5L value set for China. *Value in Health, 20*(4), 662–669. https://doi.org/10.1016/j.jval.2016.11.016.

Lydick, E., Martin, A., & Yawn, B. (1996). Impact of fears on quality of life in patients with a silent disease: osteoporosis. *Clinical Therapeutics, 18*(6), 1307–1315.

Madureira, M. M., Ciconelli, R. M., & Pereira, R. M. R. (2012). Quality of life measurements in patients with osteoporosis and fractures. *Clinics (Sao Paulo, Brazil), 67*(11), 1315–1320. https://doi.org/10.6061/clinics/2012(11)16.

Martin, A. R., Sornay-Rendu, E., Chandler, J. M., Duboeuf, F., Girman, C. J., & Delmas, P. D. (2002). The impact of osteoporosis on quality-of-life: the OFELY cohort. *Bone, 31*(1), 32–36. https://doi.org/10.1016/S8756-3282(02)00787-1.

McDonald, J. H. (2009). *Handbook of biological statistics*. Baltimore, MD: Sparky House publishing.

Myles, P. S., & Cui, J. (2007). Using the Bland-Altman method to measure agreement with repeated measures. *BJA: British Journal of Anaesthesia, 99*(3), 309–311. https://doi.org/10.1093/bja/aem214%JBJA.

Osteoporosis prevention, diagnosis, and therapy (2001). *JAMA, 285*(6), 785–795, https://doi.org/10.1001/jama.285.6.785.

Pasco, J. A., Seeman, E., Henry, M. J., Merriman, E. N., Nicholson, G. C., & Kotowicz, M. A. (2006). The population burden of fractures originates in women with osteopenia, not osteoporosis. *Osteoporosis International, 17*(9), 1404–1409. https://doi.org/10.1007/s00198-006-0135-9.

Richardson, J., Iezzi, A., Khan, M. A., & Maxwell, A. (2014). Validity and reliability of the Assessment of Quality of Life (AQoL)-8D multi-attribute utility instrument. *Patient, 7*(1), 85–96. https://doi.org/10.1007/s40271-013-0036-x.
Selivanova, A., Buskens, E., & Krabbe, P. F. M. (2018). Head-to-Head comparison of EQ-5D-3L and EQ-5D-5L Health Values. *PharmacoEconomics, 36*(6), 715–725. https://doi.org/10.1007/s40273-018-0647-0.
Shen, W., Burge, R., Naegeli, A. N., Shih, J., Alam, J., Gold, D. T., et al. (2014). Psychometric properties of the osteoporosis assessment questionnaire (OPAQ) 20: Results from the multiple outcomes of raloxifene evaluation (MORE) study. *BMC Musculoskeletal Disorders, 15*, 374. https://doi.org/10.1186/1471-2474-15-374.
Si, L., Winzenberg, T., Jiang, Q., Chen, M., & Palmer, A. (2015). Projection of osteoporosis-related fractures and costs in China: 2010–2050. *Osteoporosis International, 26*(7), 1929–1937.
Si, L., Winzenberg, T. M., de Graaff, B., & Palmer, A. J. (2014a). A systematic review and meta-analysis of utility-based quality of life for osteoporosis-related conditions. *Osteoporosis International*. https://doi.org/10.1007/s00198-014-2636-2.
Si, L., Winzenberg, T. M., Graaff, B., & Palmer, A. J. (2014b). A systematic review and meta-analysis of utility-based quality of life for osteoporosis-related conditions. *Osteoporosis International, 25*(8), 1987–1997.
Silverman, S. L. (2005). Quality-of-life issues in osteoporosis. *Current rheumatology Reports, 7*(1), 39–45. https://doi.org/10.1007/s11926-005-0007-x.
Svedbom, A., Borgstom, F., Hernlund, E., Strom, O., Alekna, V., Bianchi, M. L., et al. (2018). Quality of life for up to 18 months after low-energy hip, vertebral, and distal forearm fractures-results from the ICUROS. *Osteoporosis International, 29*(3), 557–566. https://doi.org/10.1007/s00198-017-4317-4.
Walters, S. J., & Brazier, J. E. (2005). Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Quality of Life Research, 14*(6), 1523–1532.
Whitehead, S. J., & Ali, S. (2010). Health outcomes in economic evaluation: the QALY and utilities. *British Medical Bulletin, 96*(1), 5–21. https://doi.org/10.1093/bmb/ldq033%.
Yang, L. S., Shan, B. L., Shan, L. L., Chin, P., Murray, S., Ahmadi, N., et al. (2016). A systematic review and meta-analysis of quality of life outcomes after radical cystectomy for bladder cancer. *Surgical Oncology, 25*(3), 281–297. https://doi.org/10.1016/j.suronc.2016.05.027.
Zhang, Z., Ou, Y., Sheng, Z., & Liao, E. (2014). How to decide intervention thresholds based on FRAX in central south Chinese postmenopausal women. *Endocrine, 45*(2), 195–197. https://doi.org/10.1007/s12020-013-0076-y.

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