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ORIGINAL ARTICLE

Cross-geographic region differences in quality of life in women with and without vertebral fracture

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Abstract
Summary Not much is known about cross-geographic region differences in quality of life (QoL) in women with and without prevalent vertebral fractures (VFX). QoL differed between continents, countries, and ethnicities. The observed differences in QoL mostly appeared larger than the difference in QoL between women with or without mild to moderate VFX.
Introduction Quality of life (QoL) is an increasingly important outcome measure in randomized controlled trials and cost-utility studies. However, not much is known about cross-geographic region differences in QoL. The objective of this study was to describe the cross-geographic region differences in QoL in women with and without mild to moderate prevalent vertebral fractures (VFX).
Methods The study was performed using baseline data of the bazedoxifene study. The study was carried out in 25 countries in six continents (n=7117). QoL was assessed using the index and Visual Analogue Scale (VAS) scores of the EQ-5D, Qualeffo-41, and Women's Health Questionnaire (WHQ). VFX were assessed using semi-quantitative and quantitative morphometric methods.
Results In general, all four instruments followed more or less the same pattern. In most analyses, the reported QoL was lowest in Asia and Europe and highest in North America and Oceania. To examine the influence of ethnicity, North and South America were stratified on race. In both continents, a lower QoL was observed in Hispanic people.
Conclusions QoL differed between continents, countries, and ethnicities. The observed differences in QoL appeared larger between most continents and countries than the difference in QoL between women with or without mild to moderate VFX.

Keywords Cross-geographic region · Quality of life · Vertebral fracture · Women

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Introduction

It is estimated that about 16–39% of elderly persons suffer from vertebral fractures (VFX), depending on the criteria used for determination [1–6]. VFX are associated with back pain and impaired physical functioning [3, 5–9]. Furthermore, quality of life (QoL) decreases with an increasing number of VFX and with increasing severity [7, 10–15].

QoL is an increasingly important outcome measure in randomized controlled trials and cost-utility studies. Many randomized controlled trials in osteoporosis research are performed as multinational studies. These studies usually use cross-calibrated instruments to measure QoL. However, because of power limitations, most studies do not differentiate between countries or continents. Therefore, it is not clear how large the differences in QoL are between countries and continents and how these differences may

influence the observed QoL in the absence or presence of VFX.

Therefore, the objective of this study is to describe the cross-geographic region differences in QoL in women with and without prevalent VFX living in different continents and countries. Three different QoL instruments will be used: the index score and Visual Analogue Scale (VAS) score of the EQ-5D, the Qualeffo-41, and the Women's Health Questionnaire (WHQ).

Materials and methods

Design

The study was performed using screening and baseline data of the bazedoxifene study, a multicenter, double-blind, randomized controlled trial examining fracture incidence reduction and safety of bazedoxifene acetate compared to placebo and raloxifene in osteoporotic postmenopausal women. Inclusion criteria were (1) generally healthy postmenopausal women from 50 to 85 years of age, (2) at least 2 years postmenopausal, and either (3a) osteoporotic subjects without VFX (bone mineral density *T* score at the femoral neck or lumbar spine of −2.5 or worse without the presence of VFX) or (3b) osteoporotic subjects with VFX (presence of one to five mild or moderate asymptomatic VFX and a lumbar spine and femoral neck bone mineral density *T* score not worse than −3.5).

Continents and countries

The study was carried out in 29 countries in six continents: Africa (South Africa), Asia (Hong Kong), Europe, including the European side of the Russian Federation (Belgium, Bulgaria, Croatia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Lithuania, Netherlands, Norway, Poland, Romania, Russian Federation, Slovakia, Spain), North America (Canada, Mexico, USA), South America (Argentina, Brazil, Chile), and Oceania (Australia, New Zealand). For four of these countries (Estonia, Greece, Lithuania and Slovakia), no data on QoL were available and these were excluded, leaving 25 countries for the analyses (n=7117).

VFX

Thoracic and lumbar spine radiographs (T4 to L4) were obtained during screening. An anteroposterior radiograph was taken to identify the vertebra with the best accuracy; a lateral radiograph was obtained to assess VFX. A central laboratory performed a semi-quantitative assessment of all radiographs. A quantitative morphometric assessment was performed only when a VFX was observed by semi-quantitative assessment. When the semi-quantitative assessment differed from the quantitative assessment, a second reader at the central laboratory using the semi-quantitative assessment confirmed or refuted the presence of VFX.

QoL

QoL was assessed using the index score (n=6837) and the VAS score (n=6749) of the EQ-5D, the Qualeffo-41 (n=7041), and the WHQ (n=7051). The EQ-5D consists of five items scored from 1 to 3, representing the domains mobility, self-care, usual activities, pain/discomfort and anxiety/depression [16]. When combining the scores of the different items, 243 different health states can be formed. In a UK study, the time trade-off method was used to derive valuations for 42 health states, which were subsequently modeled to predict the remaining index scores [17]. The index score or utility summarizes the health state of a participant, with 0 representing death and 1 representing perfect health. In addition, the participants were asked to draw a line on a VAS scale to indicate how good or bad their own health was today. The VAS scale ranges from 0 (worst imaginable health state) to 100 (best imaginable health state).

The Qualeffo-41 has been developed as a specific instrument for measuring QoL in patients with VFX [12, 18]. It consists of 41 items in five domains: pain, physical function, social function, general health perception, and mental function. Total score ranges from 0 (high quality of life) to 100 (low quality of life).

The WHQ was originally designed to assess symptom perceptions during the menopause transition and in older postmenopausal women [19]. It has been considered a disease-specific instrument because of the focus on menopause transition. However, the questionnaire measures a wide range of domains of symptom experience: depressed mood, somatic symptoms, anxiety/fears, vasomotor symptoms, sleep problems, sexual behavior, menstrual symptoms, memory/concentration, and attractiveness. The WHQ consists of 36 items of which 34 are used to calculate QoL. The item "I worry about growing old" is not used because it was found not to contribute significantly to any of the subscales in an earlier study [20]; the item "I have heavy periods" was not considered relevant to our postmenopausal population.

All translations were developed through a comprehensive linguistic validation process: two forward translations, one backward translation, cognitive debriefing on a sample of the native language speakers and target population, and international linguistic harmonization. All translations were country specific, e.g., US Spanish, Chilean Spanish, Argentinean Spanish, Mexican Spanish, Spanish Spanish.

Table 1 Baseline differences for women without and with prevalent VFX in the different continents

Continents	No prevalent VFX	Prevalent VFX	*p* value
Africa			
Age	66.8±8.0	67.0±7.8	0.846
BMI	23.5±3.8	25.9±3.6	<0.001
Race (% white)	51 (92.7%)	158 (94.6%)	0.606
Number of persons (%)	55 (24.8%)	167 (75.2%)	
Asia			
Age	65.6±6.0	65.7±7.5	0.929
BMI	22.0±2.7	24.4±3.2	0.004
Race (% white)	0 (0%)	0 (0%)	–
Number of persons (%)	37 (62.7%)	22 (37.3%)	
Europe			
Age	65.5±6.3	67.7±6.1	<0.001
BMI	25.6±3.6	26.6±3.6	<0.001
Race (% white)	1,030 (99.6%)	1,428 (99.9%)	<0.220
Number of persons (%)	1,034 (42.0%)	1,430 (58.0%)	
Oceania			
Age	66.3±7.6	67.2±7.6	0.519
BMI	24.2±3.7	25.4±3.4	0.077
Race (% white)	34 (89.5%)	82 (100%)	0.003
Number of persons (%)	38 (31.7%)	82 (68.3%)	
S. America			
Age	65.9±6.5	66.9±6.7	<0.001
BMI	25.9±3.8	27.8±3.8	<0.001
Race (% white)	1,209 (81.9%)	1,051 (75.2%)	<0.001
Number of persons (%)	1,477 (51.4%)	1,398 (48.6%)	
N. America			
Age	65.1±6.6	65.9±7.6	0.045
BMI	25.6±3.9	27.0±4.1	<0.001
Race (% white)	331 (74.0%)	790 (84.9%)	<0.001
Number of persons (%)	447 (32.5%)	930 (67.5%)	

Presented are the means (and standard deviation) and number (and percentage). Differences in mean were tested using *T* test; differences in frequency were tested using Pearson Chi-square

VFX vertebral fracture, *BMI* body mass index

Confounders

Confounders were age, body mass index (BMI), race (Asian, Black, Hispanic, Native American, Other, Pacific Islander, White), prevalent VFX (yes/no), and severity of prevalent VFX (no fracture, one mild fracture, more than one mild fracture, any moderate fracture, any severe fracture).

Statistical analysis

First, baseline differences in age, BMI, and race were assessed for patients with and without prevalent VFX in the different continents. Because age and BMI were normally distributed, *T* test was used to examine differences in mean. For race, Pearson Chi-square test was used to examine differences in frequencies. Second, ANCOVA was performed to examine the differences in QoL between the different continents. Based on the distributions of the QoL instruments, a comparison of mean and median, a histogram of the standardized residuals, a P–P Plot of the standardized residuals, and a scatterplot of the standardized predicted values versus the standardized residuals using linear regression analyses, it was decided by a statistician that it was allowed to present mean values despite the not completely normal distribution of the index score and VAS score of the EQ-5D. ANCOVA was performed for the total population, for persons having prevalent VFX and for persons having no prevalent VFX. The first model was unadjusted; the second model was adjusted for age, BMI and race; the third model was adjusted for age, BMI, race, and severity of VFX. Because of low numbers in some of the categories, race was categorized into White (n=6164), Black (n=486), Hispanic (n=348), or other (n=119); severity of VFX was categorized into no fracture (n=3088), one mild fracture (n=2636), more than one mild fracture (n=730), any moderate, or any severe fracture (n=663). Third, bar charts were made to present the QoL in

women having VFX (yes/no) in smaller parts of Europe, i.e., North Europe (Denmark, Finland, Norway), West Europe (Belgium, France, Germany, Netherlands), East Europe (Bulgaria, Croatia, Hungary, Poland, Romania, Russian Federation), and South Europe (Italy, Spain); and North America, i.e., Canada/USA and Mexico. Fourth, to examine the influence of ethnicity, North and South America were stratified on race. Because of reasons of power, only ethnicities containing 100 persons or more were included in the analysis. This analysis was not possible for the other continents because these consisted mainly of one ethnicity. Fifth, countries with more than 100 persons were analyzed separately. Again, we limited the analyses to countries having 100 persons or more because of reasons of power.

Results

In Table 1, the baseline differences for women without and with prevalent VFX in the different continents are presented. Women with prevalent VFX in Europe, South America, and North America were significantly older than women without prevalent VFX. Furthermore, women with prevalent VFX in Africa, Asia, Europe, South America, and North America had a significantly higher BMI than women without prevalent VFX. Finally, women with prevalent VFX were significantly more often White in Oceania and North America and significantly less often White in South America.

In Tables 2 and 3, the QoL according to the index score of the EQ-5D and Qualeffo-41 per continent is presented. In the first instrument, a lower score represents a lower QoL; in the second instrument, a higher score represents a lower QoL. It can be seen that there are large differences between the continents with women from Africa, Asia, and Europe mostly reporting a lower QoL. When considering all four instruments (including the VAS score of the EQ-5D and the WHQ, data not shown), women from Asia and Europe mostly reported a lower QoL, and women from North America and Oceania mostly reported a higher QoL.

When comparing women with and without VFX in Tables 2 and 3, QoL was significantly lower in women with VFX in Africa ($p=0.006$ for index score and $p<0.001$ for Qualeffo-41), Asia ($p=0.043$ for index score and $p=0.037$ for Qualeffo-41), Oceania ($p=0.005$ for index score), and South America ($p=0.017$ for index score). Furthermore, QoL was significantly higher in women with VFX in Europe ($p=0.041$ for index score and $p<0.001$ for Qualeffo-41).

When dividing Europe and North America in smaller parts, it can be seen that QoL is lower (i.e., a higher score on the Qualeffo-41) in East and South Europe and in Mexico (Fig. 1). In East Europe, QoL as assessed by the Qualeffo-41 ($p=0.019$) was significantly lower in women having VFX. A borderline statistically significant lower QoL was observed in women having VFX in South Europe ($p=0.051$).

To examine the influence of ethnicity, North and South America were stratified on race (Table 4). In both South America and North America, a lower QoL was observed in Hispanic people. The other ethnicities had a significantly higher QoL as compared with Hispanic people after adjustment for age, BMI, and severity of VFX. When comparing Hispanic people living in North and South

Table 2 Quality of life in women without and with prevalent VFX by continent: results for the index score of the EQ-5D

	Africa	Asia	Europe	Oceania	S. America	N. America	*p* value
Total population							
M1	0.79	0.75	0.78*	0.84*	0.83***	0.80 (R)	<0.001
M2	0.78*	0.69**	0.78***	0.83	0.84**	0.81 (R)	<0.001
M3	0.78*	0.70**	0.78***	0.83	0.84**	0.81 (R)	<0.001
No VFX							
M1	0.86*	0.79	0.77*	0.91**	0.84***	0.80 (R)	<0.001
M2	0.85	0.76	0.77***	0.90*	0.84*	0.82 (R)	<0.001
VFX							
M1	0.77	0.69*	0.79	0.81	0.83**	0.80 (R)	<0.001
M2	0.75**	0.62**	0.78**	0.79	0.83*	0.81 (R)	<0.001
M3	0.76**	0.62**	0.78**	0.79	0.83**	0.81 (R)	<0.001

Presented are the means after adjustment for confounding variables. A lower score represents a lower quality of life. Differences in mean were tested using ANCOVA. Model 1 (M1): Unadjusted model. Model 2 (M2): After adjustment for age, BMI, race. Model 3 (M3): After adjustment for age, BMI, race, severity of VFX.

VFX vertebral fracture

*$p<0.05$; **$p<0.01$; ***$p<0.001$ as compared to the reference group (R)

Table 3 Quality of life in women without and with prevalent VFX by continent: results for the Qualeffo-41

	Africa	Asia	Europe	Oceania	S. America	N. America	*p* value
Total population							
M1	22.9**	25.6**	26.2***	18.5	26.0***	20.2 (R)	<0.001
M2	23.8***	29.9***	26.6***	19.4	25.7***	19.6 (R)	<0.001
M3	24.1***	29.6***	26.6***	19.7	25.6***	19.8 (R)	<0.001
No VFX							
M1	18.6	23.3	28.2***	16.1*	25.7***	20.5 (R)	<0.001
M2	19.5	26.2*	28.5***	17.0	25.7***	19.3 (R)	<0.001
VFX							
M1	24.4***	29.5**	24.8***	19.6	26.3***	20.1 (R)	<0.001
M2	25.5***	34.1***	25.3***	20.8	25.6***	19.8 (R)	<0.001
M3	25.4***	33.9***	25.3***	20.8	25.6***	19.8 (R)	<0.001

VFX vertebral fracture

Presented are the means after adjustment for confounding variables. A higher score represents a lower quality of life. Differences in mean were tested using ANCOVA. Model 1 (M1): Unadjusted model. Model 2 (M2): After adjustment for age, BMI, race. Model 3 (M3): After adjustment for age, BMI, race, severity of VFX

*p<0.05; **p<0.01; ***p<0.001 as compared to the reference group (R)

America, a significantly lower QoL was observed in North America (p<0.001 for the index score, VAS score, and WHQ; p<0.01 for Qualeffo-41).

In Fig. 2, countries with more than 100 participants were presented separately. When looking at the Qualeffo-41, it can be seen that QoL was highest in Canada, Denmark, the Netherlands, Norway, USA, and South Africa. The results were similar for the WHQ; the EQ-5D showed less variation (data not shown).

Discussion

In this study, it was shown that QoL differs between continents and countries. In general, QoL appeared lowest in Asia and Europe and highest in North America and Oceania. When dividing North and South America in different ethnicities, it was seen that QoL appears lower in Hispanic people. The differences between continents, countries, and ethnicities appeared larger than the differences in Qol between women with or without mild to moderate VFX.

When interpreting the results of this paper, it is important to keep in mind that the phrases “low QoL” and “high QoL” are based on the scores of questionnaires. We think it is only possible to assess cross-geographic region differences and not to assess which country, continent, or ethnicity truly has the lowest QoL. It can only be assessed which ones have the worst scores on the included QoL instruments. QoL may be influenced by several other mechanisms not covered by the QoL instruments.

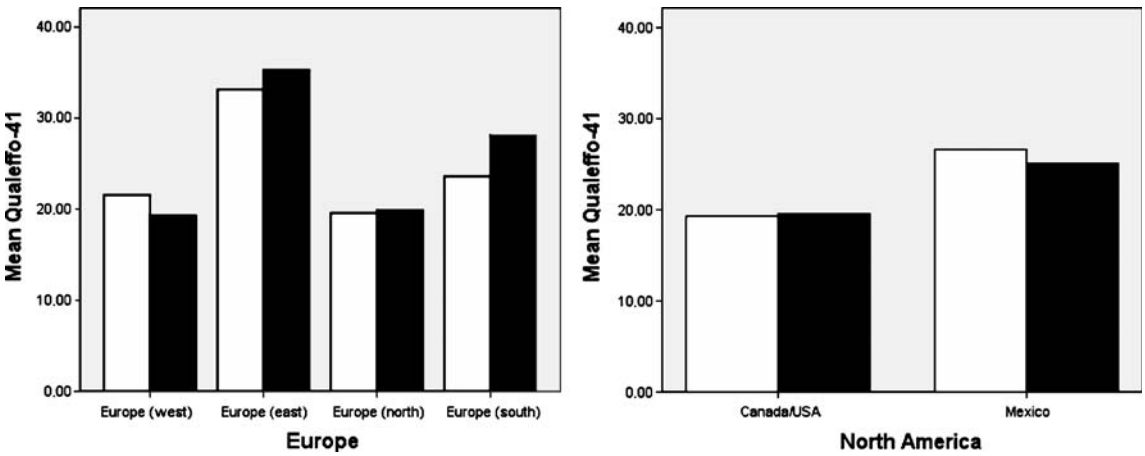

Fig. 1 Quality of life after vertebral fracture according to Qualeffo-41 in Europe and North America. *White bars* “No prevalent fracture”; *black bars* “at least one prevalent vertebral fracture”

Table 4 The influence of ethnicity on quality of life

Total population	Index score of the EQ-5D	VAS score of the EQ-5D	Qualeffo-41	WHQ
N. America				
Hispanic	0.76**	79.5	24.6***	0.37***
White	0.81 (R)	81.9 (R)	19.3 (R)	0.25 (R)
p value	0.001	0.073	<0.001	<0.001
S. America				
Hispanic	0.63***	72.1***	33.0***	0.51***
Black	0.86	82.6	26.8*	0.40*
White	0.84 (R)	81.3 (R)	25.5 (R)	0.39 (R)
p value	<0.001	<0.001	<0.001	<0.001

Presented are the means after adjustment for confounding variables (age, body mass index, and severity of prevalent vertebral fractures). For the Index and VAS scores, a lower score represents a lower quality of life; for the Qualeffo-41 and WHQ, a higher score represents a lower quality of life. Differences in mean were tested using ANCOVA

WHQ Women's Health Questionnaire

*$p<0.05$; **$p<0.01$; ***$p<0.001$ as compared to the reference group (R)

The finding that Hispanic women had lower QoL supports another study. In a study examining the association between QoL and early perimenopause and ethnicity (Black, Chinese, Hispanic, Japanese, and White), a lower mean QoL was found in Hispanic women for the role-physical, bodily pain, vitality, role-emotional, and social function domain of the SF-36 [21]. After adjustment for socioeconomic status, health, lifestyle, and social circumstances, ethnicity remained significant for bodily pain and social functioning. According to the authors, this may indicate that there are true ethnic/cultural differences in QoL, that important predictors of QoL have not yet been included in the analyses, or that there are ethnic or cultural differences in how some questions are interpreted, in the meaning of health constructs, or in what answers are socially acceptable.

In the same study, however, a higher mean QoL was found in Japanese and Chinese women [21]. This seems to contradict our finding that women living in Asia had lower QoL. In another study examining the experience of menopause and QoL, Asian women living in India and Asian women living in the UK reported a lower QoL as assessed by the WHQ than Caucasian women living in the UK [22]. Interestingly, Asian women living in India reported fewer menopausal symptoms as compared to the other two groups. In a third study, Japanese men and women (mean age, 43.5) without chronic disease had a significantly lower mean physical summary component

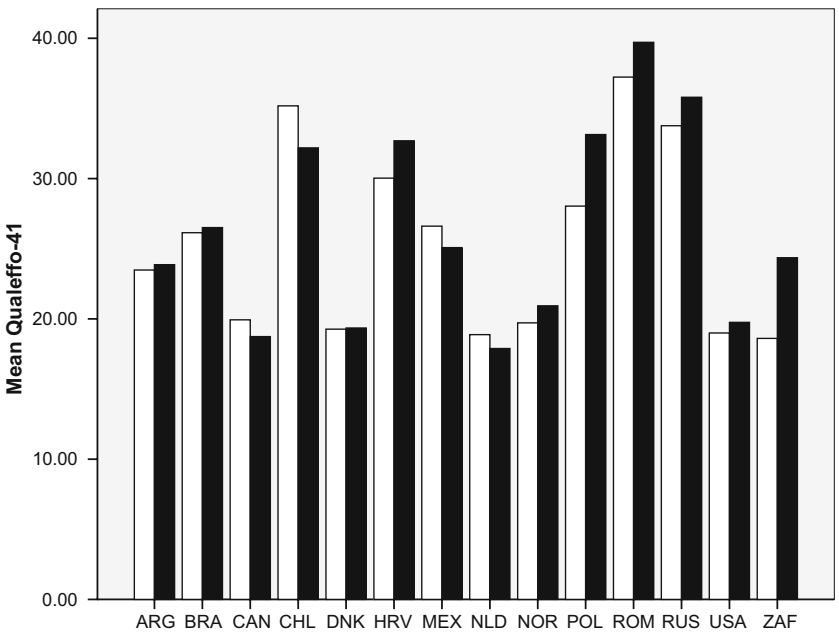

Fig. 2 Quality of life after vertebral fracture according to Qualeffo-41 in countries with more than 100 participants. *White bars* "No prevalent fracture"; *black bars* "at least one prevalent vertebral fracture"

score of the SF-36 as compared to US men and women (mean age, 43.6); no significant difference was found for the mental summary component score [23].

The differences in QoL between some countries may be explained by differences in socioeconomic status. This may be reflected by the lower QoL in East and South Europe in Fig. 1, for example. Also, other confounding variables such as marital status may play a role. Unfortunately, these data were not available in this study. We did perform some additional analyses using gross domestic product per capita (GDP) as a marker for socioeconomic status. For each country, GDP was searched in current US dollars in The World Economic Outlook (WEO) Database April 2003 (www.imf.org/external/pubs/ft/weo/2003/01/data/index.htm). When additionally adjusting the final models in Table 2 for GDP, the index scores of the EQ-5D were similar to the final models (data not shown). When adjusting the final models in Table 3 for GDP, Qualeffo-41 scores were lower in Africa and South America and higher in Asia and North America (data not shown). Using GDP as a marker for socioeconomic status has an important limitation. The data were not available at the individual level and, therefore, not very specific. Especially in the USA, a high within-country variation is expected, while in Europe, a high between-country variation is expected. Future studies are needed to explain whether part of the differences in QoL may be explained by socioeconomic status.

An important consequence of our findings is that multinational studies with QoL as an outcome measure should take into account continent, country, and ethnicity. When the research aim is to compare persons with and without VFX, it is important that in each continent or country and for each ethnicity sufficient persons with and without VFX are included. If this is not possible, it may be important to stratify the results on or adjust for continent, country, or ethnicity.

An unexpected finding was that a significantly higher BMI was found in women with prevalent VFX in Africa, Asia, Europe, North America, and South America as compared to women without prevalent VFX. This may be due to the inclusion of mild to moderate VFX only. As expected, in the studied population, BMI is positively correlated with bone mineral density (personal communication with N. Kuchuk, 2007). Also, the finding that QoL was significantly higher for those with VFX in Europe may be explained by the fact that mild to moderate prevalent vertebral fractures were included in this study. Some of these fractures may have been present for a long time, and some of these were subclinical.

A strength of this study is that this may be the only osteoporosis study in which the QoL is presented for six different continents containing 25 different countries. Limitations include that not all countries had sufficient number of women to analyze them separately, that the number of women in Asia was low, and that it was not possible to adjust for many confounders. Furthermore, due to the inclusion criteria of this study, only mild to moderate VFX were included.

In future research, it would be interesting to examine the causes for the observed cross-geographic region differences. As was seen in the study of Avis et al., part of the differences can be explained by socioeconomic status, health, lifestyle, and social circumstances [21]. However, this was not true for all domains of the SF-36, and it is not clear if these variables can explain the differences as were found for the EQ-5D, Qualeffo-41, and WHQ. Qualitative research may give additional explanations for the observed differences in QoL. It may be that different priorities exist in different continents/countries or for different ethnicities. As a consequence, it may be necessary to weigh the subscales differently or to add extra domains or items for certain continents/countries/ethnicities. Also, it is possible that certain subgroups are more positive, negative, or extreme to both sites in answering questionnaires.

In conclusion, QoL differed between continents, countries, and ethnicities. The observed differences in QoL appeared larger between most continents and countries than the difference in QoL between women with or without mild to moderate VFX indicating that attention is needed for this issue in the design or analysis stage of multinational studies.

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