ORIGINAL RESEARCH ARTICLE

Population-based norms for the human papillomavirus-quality of life (HPV-QoL) questionnaire: A cross-sectional multicenter study

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Abstract

Introduction: Human papillomavirus (HPV) diagnosis has a considerable emotional and psychological impact on women. To evaluate the impairment this infection leads to regarding quality of life (QoL), several scales have been suggested, such as the human-papillomavirus-quality-of-life (HPV-QoL) questionnaire. This has been validated for the Spanish population and measures the impact of HPV on health-related-quality-of-life (HR-QoL). However, normative values are yet to be developed. Thus, the objective was to describe the population-based norms of the HPV-QoL for Spanish women aged 25–65 years and to test the questionnaire's construct validity.

Material and Methods: This was a cross-sectional nationwide multicenter study. Women from outpatient clinics in Spain aged 25–65 years, with a diagnosis of past or active HPV infection were recruited. The central tendency, dispersion, and percentiles were calculated for the total score and its dimensions for each age group. Construct validity was tested by analyzing age groups and their correlations with other related scales (12-Item General Health Questionnaire [GHQ-12], Female Sexual Function Index [FSFI], and Hospital Anxiety and Depression Scale [HADS]).

Results: A total of 1352 women were included in the study. The norms showed moderate and significant coefficients of correlation with other related scales. Significant differences between age strata groups were found according to educational level, sexual dysfunction, sexual activity, mental deterioration, and severity of anxiety and depression symptoms ($p < 0.001$ in all cases). The total score differed significantly between the groups ($p = 0.006$). Significant differences in the contagiousness, health, and sexuality dimensions ($p < 0.05$) were found among the groups. It was seen that HPV infection impaired women's QoL. Dimensions within all test age groups ($p < 0.001$ in all cases) were significantly different, with the health dimension being the highest

contributor to women's QoL impairment, whereas social well-being was the main determinant of QoL.

Conclusions: Population-based norms for the novel HPV-QoL questionnaire showed adequate validity and could be a useful tool for assessing the impact of QoL among women with HPV in Spain.

KEYWORDS
HPV, patient-reported measures, sexuality, statistics, Women's health issues

1 | INTRODUCTION

Human papillomavirus (HPV) is the most widespread sexually transmitted viral infection worldwide and is a causative agent of cervical cancer and precancerous lesions such as low- and high-grade squamous intraepithelial lesions.[1,2] To prevent HPV-related lesions in the lower genital tract, population-based screening programs for women aged 21–65 years have been implemented in some countries.[3] Some studies have documented psychological reactions in women after being informed of their HPV diagnosis.[4–8] An abnormal cytology result is frequently associated with anxiety, insomnia, stigmatization, fear of cancer, changes in sexual behavior or body image, and even delusions.[4] In addition, women with HPV often feel worried about sharing their screening results with others, thus worsening their emotional relationship with their partners and exacerbating their existing sexual problems. Concerns about HPV tests and treatments have also been reported, along with dissatisfaction with the information provided by their doctors.[4–8]

The human-papillomavirus-quality-of-life (HPV-QoL) questionnaire was developed to assess health-related quality of life (HRQOL) in women with past or present HPV infection, assessed with an HPV DNA cervical test positive for either high- or low-risk lesions (classified as ICD-10-CM as R87.810 and R87.820, respectively). This questionnaire has been validated for the Spanish population.[9] It is a self-administered, multidimensional, and innovative tool that includes several domains that evaluate the impact of HPV infection on women regarding their daily living, general health, feelings, and behaviors. It consists of 15 questions in four domains: general well-being, psychological well-being, sexuality, health, and contagiousness. The scale measures the quality of life (QoL), with a score ranging from 0 (worst quality of life) to 100 (best quality of life). The HPV-QoL questionnaire aims to improve counseling and enhance women's QoL to achieve a better psychological response and health outcomes.[9] To our knowledge, normative scales or population reference standards have not yet been defined for this questionnaire, an attribute that is relevant in measuring the impact on HRQOL in women with HPV infection,[10–12] as they provide a reference for comparing the differences in health status between various pathologies or treatments and to monitor the effectiveness of therapeutic interventions in a certain population.[13] Moreover, they can be used to evaluate the benefit of health interventions, as with other existing questionnaires, since they compare women who participate

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Key message

Several scales assess impairment in the quality of life caused by HPV infection. By obtaining population-based norms, age-focused strategies can facilitate health decision-making. This is the first study to develop the normative values in a questionnaire specifically designed for HPV infection.

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in the questionnaire in relation to their reference population.[13,14] By developing HPV-QoL normative values, we aimed to detect the dimensions responsible for QoL impairment after HPV diagnosis in different age groups, as this would allow the design of counseling strategies to deal with QoL deterioration specifically targeted to certain stages of life.

Therefore, the objective of this study was to develop, for the first time, reference population-based norms of the HPV-QoL questionnaire in women aged 25–65 years in Spain and to test its construct validity.

2 | MATERIAL AND METHODS

2.1 | Study design and population

This cross-sectional, multicenter, nationwide study included participants from all 17 regions of Spain. The Clinical Research Ethics Committee approved the study protocol. All participating centers approved the protocol for patient recruitment, and all participants in the study were required to provide informed consent. This nationwide study was conducted between January 2022 and January 2023 in gynecology clinics throughout Spain. The distributions of age and educational level were similar between our sample and the whole of Spain. Additionally, all Spanish regions were included (Supporting Information Tables S1). As the new instrument aims to measure the impact of HPV infection on HRQoL, its norms are based on the selection of adult women with a history of past or current HPV infection. All participating women were informed about their last HPV test results. Women with a negative HPV test and no previous positive test, or those in whom an HPV test had never been

performed, were not included, as the HPV-QoL questionnaire only applies to women with a history of HPV infection in the lower genital tract. Based on the incidence of HPV and cervical lesions, as well as recommendations for cervical cancer screening, we collected data from women aged 25–65 years.[3] The authors have received no specific funding for this study.

Participants met the following inclusion criteria: women from outpatient clinics ranging in age from 25 to 65 years, with past or active HPV infection diagnosis irrespective of previous vaccination against HPV, ability to understand and answer the health questionnaires included in the study edited in Spanish (Spain), and willingness to sign an informed consent form. We excluded women who were pregnant, those with a recent diagnosis of any malignancy, and those with psychiatric disorders with poorly controlled symptoms. The questionnaire was distributed during daily clinical practice, and information or counseling about HPV was provided after it was completed to avoid possible changes in the participants' feelings or perceptions about HPV. The size of the recruited sample, which was considered adequate (a posteriori) to develop population norms, was based on the rule of ensuring a minimum of two participants for each possible point of measurement (percentile) and for each age stratum (seven age strata). In addition, the sample size calculation considered the expected difference in the prevalence of HPV infection between premenopausal and peri/postmenopausal women, which is approximately 4:1 in Spain.[15] Sample size was increased by an additional 5% to protect the study against possible missed data.[16] Under these considerations, the final sample size of 1352 women (92% of the a priori determined theoretical sample size) was nonetheless considered sufficient.

2.2 | Health outcome measures for testing construct validity

The construct validity of the norms was tested to grant its robustness and validity and was assessed by means of two approaches, as carried out by other authors.[16–18] First, a correlation analysis was conducted for the HPV-QoL questionnaire, total score, dimensions, and subdomains: general well-being, psychological well-being, social well-being, health, sexuality, and contagiousness. Correlation coefficients were calculated between HPV-QoL and the Hospital Anxiety and Depression Scale (HADS), Female Sexual Function Index (FSFI), and 12-item General Health Questionnaire (GHQ-12) to explore anxiety and depression status as well as mental and sexual functioning. It was hypothesized that the HPV-QoL would have a statistically significant and moderate correlation with the total scores of the HADS, FSFI, and GHQ-12 questionnaires, with a correlation coefficient between 0.3 and 0.7.[10,11,18,19] The correlation between HPV-QoL and both HADS and GHQ-12 was expected to be negative because the higher the score on the HPV-QoL questionnaire (better QoL), the lower the anxiety/depression scores, and the lower the impact on women's self-esteem, stress, and coping. In contrast, it was hypothesized that correlations would be positive and moderate between HPV-QoL and the FSFI score, particularly between the

sexuality domain of the HPV-QoL and its total score and the dimensions of FSFI. Spanish-validated versions of these instruments were used.[20–22]

The second strategy focused on the comparison of known groups established by separating the population of women into several groups according to the response criteria of several patient-reported outcome (PRO) instruments (FSFI, GHQ-12, and HADS), educational level (primary school, high school/vocational training, and university), sexual activity, and HPV infection status (past or present). These PRO instruments are the HADS anxiety and depression subscales, which are both categorized into three groups according to the severity of anxiety or depressive symptoms: none, mild, and moderate to severe. Participants were also classified into two categories according to their responses to the GHQ-12 (mental deterioration, yes/no; cutoff point ≥17 points for mental deterioration) and FSFI (sexual dysfunction, yes/no; cutoff point ≤26.55 for sexual dysfunction).[20–24] Sexual activity was categorized into three categories: none, occasional, and regular.

2.3 | Statistical analyses

First, a descriptive analysis was conducted on sociodemographic and clinical variables. Pearson moment coefficients of correlation were computed to test the construct validity of the HPV-QoL norms. Known group comparisons were performed with ANOVA using the robust Welch and Brown-Forsythe tests in cases where no homogeneity of variance was observed according to Levene's test. To estimate the magnitude of the mean differences between groups, the effect size (ES) was estimated with a 95% confidence interval (CI). As recommended, ES was obtained as the difference between the means divided by the combined standard deviations in variables with two groups or between the extreme categories for variables with more than two categories. ES values of 0.2, 0.5, and 0.8 were interpreted as small, moderate, or large size effects, respectively, following the recommendations of Kazis et al.[25] The statistical power was greater than the 80% required to detect small effect size differences (>0.2) in the analysis of construct validity. The significance level was set at $p < 0.05$.

To construct the population norms of the HPV-QoL questionnaire, the total sample was divided into seven age strata of 5 years (25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–65 years), except for the interval at the higher extreme, which was a stratum of 10 years (55–65 years), because of the lower number of participants in this stratum. It was expected that the 5-year distribution would provide a priori sufficient number of participants in each stratum to construct the norms of the questionnaire and a satisfactory sample size to obtain the construct validity of the questionnaire.[13,15,16] For each age group, the mean values, standard deviations and the 5, 10, 25, 50, 75, 90, and 95 percentiles of the HPV-QoL questionnaire scores were calculated for the total score and each of its dimensions. Each percentile indicates (after ranking the data from lowest to highest) the percentage of HPV-QoL scores obtained by women (for both the total and dimensions) that would be expected to fall

under that value in the Spanish population. Since a lower score on the questionnaire (both the total score and that of each dimension) is interpreted as a higher impact/interference in women's HRQOL, the calculated percentiles ease a clinical interpretation based on the variation of the total scores between the calculated percentiles plus/minus one times the standard error of measurement (SEM). SEM was considered the best estimator of the minimal important difference (MID),[26–28] which, in the case of the total score of the HPV-QoL questionnaire, is 6.1 points or 6.1%.[9] The MID corresponds to the minimum variation in the scale score that the woman can perceive when a change in her health status or HRQOL has happened and, therefore, is clinically important.[26–28] Statistical analyses were performed using IBM SPSS version 26.0, NY, USA (https://www.ibm.com/analytics/spss-statistics-software).

3 | RESULTS

A total of 1598 women were initially included in this study. There were 58 women who declined to participate in the study and did not sign an Informed Consent form. Finally, 1352 adult women were recruited (80.4% premenopausal, 19.6% peri/postmenopausal). We excluded 188 women; 105 did not meet the age criteria, 51 who had incomplete data preventing scale scoring, and 32 who had invariant responses (no variation) rendering them unreliable (Figure 1). This resulted in a response rate of 90.6% for 1, 493 eligible women, accounting for exclusions. Furthermore, we recruited a representative number of participants from every Spanish region (Supplementary Tables S1–S4) based on the proportion of women living in each
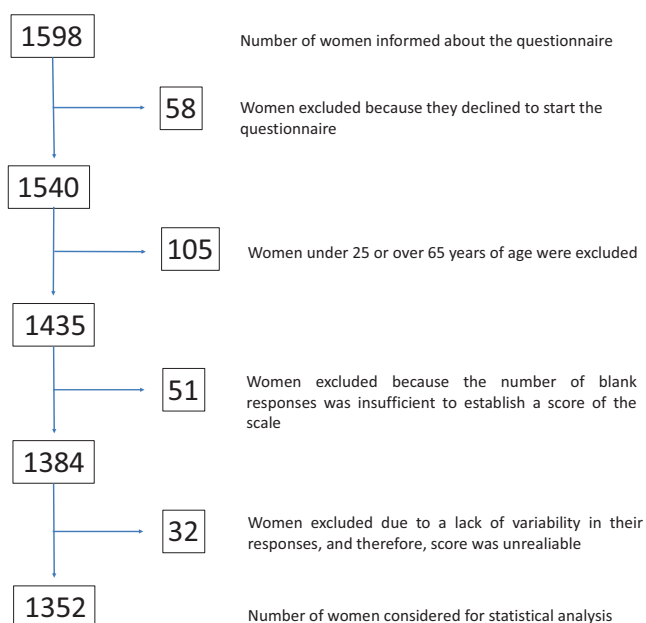
FIGURE 1 Flow chart of the included and excluded women in the study.

TABLE 1 Demographic and clinical data of women (n = 1352) included in the development of the population-based norms for the HPV-QoL questionnaire.

Characteristic	Mean (SD), %
Age (years), mean (SD), n = 1352	39.1 (9.6)
Age group (%)	
25–29	16.3
30–34	22.1
35–39	19.7
40–44	15.2
45–49	11.3
50–54	7.6
55+	7.8
BMI (kg/m²), Mean (SD), n = 1198	24.0 (8.1)
Nonobese (<30) (%)	91.8
Obese (≥30) (%)	8.2
Smoking (1 or more cigarettes per day) (%), n = 1286	15.4
Daily alcohol consumption (%), n = 1286	2.4
Educational level (%), n = 1246	
Primary	8.3
High school/LT	32.0
University	59.6
Gestations (%), n = 1266	
0	53.1
1	19.7
2+	27.2
Deliveries (%), n = 1265	
0	59.6
1	20.9
2	15.0
3+	4.5
Menopause status (%), n = 1284	
No	80.4
Peri	5.6
Post	14.0
Sexual activity (%), n = 1277	
No	16.8
Occasional	21.5
Regular	61.7
Immunosuppression (%), n = 1246	
No	92.1
Yes	4.2
HIV	3.7
Active HPV infection (%), n = 1263	
No	23.7
Yes	76.3
Previous STI (%), n = 1275	
No	85.1
Yes	14.9
Contraception (%), n = 1277	
No	29.7
Yes	70.3

(Continues)

TABLE 1 (Continued)

Characteristic	Mean (SD), %
HPV vaccination (%), n = 1279	
No	43.1
Yes	56.9

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; HPV, human papilloma virus; LT, labor trainee; STI, sexually transmitted infection; SD, standard deviation.

region. Table 1 presents the sociodemographic and clinical data of the women included in this study. Tables 2 and 3 confirm the construct validity of the HPV-QoL questionnaire using the total score and each dimension.

HPV-QoL showed moderate and negative (from −0.559 to −0.341) coefficients of correlation in both subscales of the HADS, demonstrating that the lower the score for anxiety or depression severity of symptoms, the higher the punctuation in the total score and dimensions of the HPV-QoL questionnaire (Table 2). Similar significant negative correlations (from −0.562 to −0.302) were obtained between HPV-QoL and GHQ-12. In contrast, the HRQoL total score and the sexuality domain were significantly correlated with the FSFI total score, showing positive correlation coefficients of 0.348 and 0.455, respectively (Table 2). These coefficients support the construct validity of the HPV-QoL normative scales, as they show a value different from 0, indicating a statistically significant relationship between the HPV-QoL scale and the external variables with which it is supposed to have such a connection. These variables were evaluated using the GHQ-12-, FSFI-, and HADS-validated scales. The other dimensions of HPV-QoL were also positively correlated with HPV-QoL; however, the coefficients were poor in most cases, as expected. Known-group analyses confirmed the construct validity of the questionnaire (Table 3). Significantly different scores on the HPV-QoL, both for the total and dimension scores, were observed in each of the criteria used to test known group validity, with effect sizes of small magnitude for educational level, sexual dysfunction, and sexual activity (effect size is below 0.5, in all cases, Table 3), whereas the differences were of large magnitude in the case of mental deterioration and severity of anxiety or depression symptoms (effect sizes above 1.0, Table 3). The only criterion that showed no significant differences was the comparison between past and present HPV infections, except for the health dimension, which was slightly lower in women with present infections than in those with past infections.

Table 4 displays the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles and the mean and standard deviations of the total score and dimensions of the HPV-QoL questionnaire for each age group and total sample. Figure 2 displays the values of the percentiles of the total score of the HPV-QoL scale population norms represented graphically with traffic light color coding to facilitate clinical interpretation and to position an individual woman in the corresponding age range. The total score differed significantly between age groups (Figure 3), as did the dimensions of contagiousness, health, and sexuality. On average, the total score was less than 50% of the best possible punctuation

TABLE 2 Construct validity of the population-based norms for HPV-QoL: correlation (Pearson's r coefficient) HPV-QoL questionnaire, total score and dimensions, with a total score of the HADS, FSFI, and GHQ-12 questionnaires.

	HPV-QoL questionnaire						
	General well-being	Psychological well-being	Social well-being	Contagiousness	Health	Sexuality	Total score
HAD scale							
Anxiety	−0.556	−0.525	−0.469	−0.341	−0.416	−0.417	−0.538
Depression	−0.537	−0.491	−0.481	−0.376	−0.402	−0.471	−0.559
FSFI total score	0.265	0.221	0.283	0.131	0.170	0.455	0.348
HGHQ-12 total score	−0.562	−0.522	−0.489	−0.302	−0.371	−0.442	−0.542

Abbreviations: HADS, Hospital Anxiety and Depression Scale; FSFI, Female Sexual Function Index; GHQ-12, General health questionnaire-12 items. All Pearson's r coefficients were significant at $p < 0.001$.

TABLE 3 Construct validity of the population-based norms for the HPV-QoL questionnaire: known group comparisons of the mean score of the questionnaire (dimensions and total score) according to various health outcomes along with clinical and sociodemographic variables.

Variable	n	HPV-QoL[a] questionnaire						
		General well-being	Psychological well-being	Social well-being	Contagiousness	Health	Sexuality	Total score
Educational level								
Primary	104	48.0 (2.7)	37.1 (2.7)	69.9 (3.5)	43.8 (2.8)	17.2 (2.0)	52.1 (3.3)	40.3 (1.9)
High school /labor trainee	399	53.0 (1.3)	41.8 (1.4)	75.3 (1.4)	42.6 (1.3)	18.9 (1.1)	52.8 (1.7)	41.8 (1.1)
University	743	57.3 (0.9)	45.9 (1.0)	80.2 (0.9)	50.4 (0.8)	24.4 (0.8)	61.7 (1.1)	48.5 (0.7)
ES (95% CI)[a]		0.38 (0.16-0.60)	0.32 (0.10-0.55)	0.40 (0.17-0.52)	0.30 (0.08-0.52)	0.33 (0.11-0.55)	0.32 (0.10-0.54)	0.43 (0.21-0.65)
p-value		p<0.001	p<0.001	p=0.001	p<0.001	p<0.001	p<0.001	p<0.001
HPV infection								
Past	283	55.2 (1.5)	44.9 (1.7)	75.9 (1.6)	49.9 (1.4)	25.0 (1.4)	59.2 (1.7)	47.3 (1.2)
Present	909	55.1 (0.8)	43.4 (0.9)	78.5 (0.9)	46.8 (0.8)	21.2 (0.7)	57.4 (1.1)	45.1 (0.7)
ES (95% CI)		NA	NA	NA	NA	0.18 (0.04-0.31)	NA	NA
p-value		p=0.941	p=0.424	p=0.144	p=0.052	p=0.010	p=0.385	p=0.100
Sexual dysfunction								
No	508	61.4 (1.0)	49.7 (1.1)	84.8 (0.9)	51.7 (1.0)	25.5 (0.9)	72.4 (1.1)	52.7 (0.7)
Yes (FSFI ≤26.55)	555	48.8 (1.1)	37.6 (1.1)	71.2 (1.2)	43.5 (1.0)	17.9 (0.9)	44.5 (1.3)	38.7 (0.8)
ES (95% CI)		0.53 (0.41-0.65)	0.46 (0.34-0.58)	0.53 (0.41-0.65)	0.35 (0.23-0.47)	0.37 (0.24-0.49)	1.00 (0.88-1.12)	0.77 (0.65-0.89)
p-value		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Sexual activity								
No	214	47.2 (1.9)	35.8 (2.1)	70.0 (2.2)	42.5 (1.7)	16.4 (1.3)	40.5 (2.2)	36.7 (1.4)
Occasional	275	55.9 (1.6)	45.2 (1.7)	77.5 (1.6)	48.4 (1.5)	23.6 (1.4)	56.0 (1.9)	46.0 (1.2)
Regular	788	57.2 (0.9)	45.6 (1.0)	80.4 (0.9)	48.7 (0.9)	23.3 (0.8)	63.7 (1.1)	48.2 (0.7)
ES (95% CI)		0.41 (0.26-0.57)	0.36 (0.21-0.52)	0.40 (0.21-0.56)	0.26 (0.11-0.42)	0.32 (0.17-0.48)	0.79 (0.63-0.94)	0.60 (0.45-0.76)
p-value		p<0.001	p<0.001	p<0.001	p=0.005	p<0.001	p<0.001	p<0.001
Mental deterioration								
No	891	61.4 (0.7)	50.1 (0.9)	83.9 (0.7)	50.4 (0.8)	25.4 (0.7)	64.7 (1.0)	50.5 (0.6)
Yes (GHQ-12 ≥17)	271	35.5 (1.3)	23.8 (1.3)	58.9 (1.9)	37.7 (1.5)	10.7 (0.9)	36.3 (1.8)	30.1 (1.0)
ES (95% CI)		1.17 (1.04-1.31)	1.05 (0.95-1.19)	1.04 (0.90-1.17)	0.55 (0.42-0.69)	1.15 (1.02-1.29)	0.71 (0.57-0.84)	0.99 (0.86-1.13)
p-value		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Anxiety (HADS)								
No (0-7 points)	185	62.1 (1.6)	51.8 (1.9)	82.8 (1.6)	55.6 (1.6)	27.6 (1.6)	63.2 (2.1)	52.1 (1.4)
Mild (8-10 points)	93	49.3 (2.1)	36.6 (2.2)	74.7 (2.6)	48.8 (2.3)	17.9 (1.9)	53.5 (2.9)	42.4 (1.6)

(Continues)

TABLE 3 (Continued)

Variable	n	General well-being	Psychological well-being	Social well-being	Contagiousness	Health	Sexuality	Total score
Moderate-to-severe (11–21 points)	134	33.3 (1.9)	22.1 (1.8)	55.8 (2.7)	39.6 (1.9)	9.4 (1.3)	34.5 (2.4)	29.2 (1.4)
ES (CI 95%)		1.34 (1.11–1.56)	1.26 (1.03–1.48)	1.03 (0.81–1.26)	0.72 (0.50–0.95)	0.93 (0.71–1.15)	1.01 (0.78–1.23)	1.28 (1.06–1.50)
p-value		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Depression (HADS)								
No (0–7 points)	324	55.0 (1.3)	43.7 (1.4)	77.7 (1.4)	51.6 (1.2)	22.7 (1.2)	57.3 (1.6)	46.7 (1.0)
Mild (8–10 points)	49	35.0 (3.1)	24.4 (3.0)	56.4 (4.3)	41.3 (3.4)	8.9 (1.9)	35.5 (3.5)	30.2 (2.4)
Moderate-to-severe (11–21 points)	39	25.7 (3.3)	15.4 (2.9)	46.5 (5.6)	35.6 (3.4)	5.6 (1.9)	25.2 (4.7)	23.0 (2.6)
ES (CI 95%)		1.29 (0.96–1.63)	1.13 (0.79–1.46)	1.21 (0.88–1.55)	0.72 (0.38–1.05)	0.83 (0.50–1.16)	1.09 (0.76–1.42)	1.28 (0.95–1.61)
p-value		p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

Abbreviations: ANOVA, analysis of variance; CI, confidence interval; ES, effect size according to Cohen's d: 0.20 (small), 0.50 (medium), 0.80 (large); FSFI, female sexual function index; HADS, Hospital anxiety and depression scale; HPV, human papillomavirus; NA, not applicable; QoL, quality of life;

[a]Values are expressed as means (standard error).

(45.8%; Table 4 and Figure 2). This means that, on average, 50% of the included women experienced an interference in their QoL of 54.2% or more, ranging from 57.3% in the 50–54 years age group to 50% in the 40–44 years age group. Significant differences were observed between dimensions within all test age groups; the health dimension was the highest contributor to women's QoL impairment (<25% in all age groups), while social well-being was the main determinant of QoL, with 75% or higher of the best possible score in all age groups (Table 4).

4 | DISCUSSION

The present study sets the population-based norms for the HPV-QoL questionnaire in women with past or present HPV infection. With the recruited sample, evidence was found for the construct validity of the HPV-QoL questionnaire based on the existence of moderate but statistically significant correlations with the scores of the GHQ-12, FSFI, and HAD scales. However, the significant associations provided by the correlation coefficients do not necessarily imply clinical relevance.

The strong contribution of the Health Dimension to QoL impairment is likely linked to the fear of cervical cancer associated with a positive HPV test result. This poses a significant threat to women as it is a frequently occurring cancer and one of the most common causes of cancer-related deaths among women.[29,30] Sexuality was the second most relevant contributor to the total score. Its role in QoL impairment was more important than in general well-being, except in the 50–54 and 55–65 age groups. This is consistent with previous studies as younger women typically reported being more satisfied with their romantic relationships, whereas older women reported stronger sexual dissatisfaction.[31] Furthermore, the calculated values for the 10th, 25th, 50th, 75th, and 90th percentiles of the total score for the overall sample differed by more than 6.1 points. This value indicates the SEM for the HPV-QoL scale, meaning that an increase or decrease in the HPV-QoL scale score of 6.1 or more points provides a change in the HRQoL that would be self-perceived as a real change in health.

The HPV-QoL normative values reflect the decrease in QoL among women with HPV infection living in Spain from what would be expected within their age group. Moreover, they provide information about the spheres most likely to be affected in women with HPV infection in Spain and the relevance of each sphere in QoL impairment. This scale can help identify women who are more amenable to implementing strategies to treat psychological concerns related to HPV, thus aiding in the creation of national programs aimed at increasing the QoL in this population. Owing to their domains, these prevention strategies could focus on fields that mostly justify the decrease in QoL, such as the health dimension. Consequently, this scale is useful not only for physicians in their daily clinical practice but also for health authorities in decision-making.

This is the first study to evaluate the full spectrum of HRQoL deterioration in women infected with HPV. The norms were obtained from a nationwide representative sample of women from all Spanish regions, according to their population density and sociodemographic

TABLE 4 Spanish population-based norms for the dimensions and total score of the human papillomavirus-quality-of-life (HPV-QoL) questionnaire according to age groups.

| | | Dimension | | | | | | |
| | | General well-being | Psychological well-being | Social well-being | Contagiousness | Health | Sexuality | Total score |
Age group	Percentile							
25–29 years (n=221)	5	8.3	0.0	12.5	0.0	0.0	0.0	11.9
	10	20.4	6.3	25.0	0.0	0.0	7.5	16.6
	25	34.4	18.8	53.1	25.0	0.0	33.3	28.1
	50	50.0	37.5	75.0	50.0	12.5	58.3	43.8
	75	70.8	56.3	100.0	62.5	31.3	75.0	51.0
	90	83.7	81.3	100.0	62.5	50.0	100.0	70.4
	95	91.7	87.5	100.0	75.0	56.3	100.0	75.4
	Mean (SD)	51.2 (24.3)	39.5 (25.7)	74.5 (28.5)	43.4 (22.4)	19.3 (20.5)	53.4 (30.5)	41.8 (18.8)
30–34 years (n=299)	5	12.5	0.0	25.0	0.0	0.0	0.0	13.5
	10	24.6	12.5	37.5	0.0	0.0	16.7	20.8
	25	36.5	25.0	62.5	37.5	0.0	33.3	30.2
	50	54.2	43.8	87.5	50.0	15.6	66.7	45.8
	75	75.0	68.8	100.0	62.5	31.3	83.3	59.5
	90	87.5	81.3	100.0	75.0	50.0	100.0	72.4
	95	95.8	93.8	100.0	87.5	68.8	100.0	81.3
	Mean (SD)	55.3 (24.6)	43.9 (27.0)	78.2 (26.8)	45.4 (24.3)	20.3 (21.7)	61.8 (30.7)	45.7 (20.1)
35–39 years (n=266)	5	12.5	0.0	25.0	0.0	0.0	0.0	13.1
	10	21.7	6.3	37.5	25.0	0.0	16.7	21.9
	25	41.7	25.0	75.0	37.5	0.0	33.3	33.3
	50	58.3	43.8	87.5	50.0	18.8	66.7	48.4
	75	75.0	68.8	100.0	62.5	37.5	91.7	61.5
	90	91.7	87.5	100.0	75.0	56.3	100.0	75.0
	95	100.0	100.0	100.0	87.5	75.0	100.0	84.3
	Mean (SD)	56.8 (25.1)	45.8 (27.9)	78.8 (25.9)	50.4 (23.0)	23.1 (22.2)	61.1 (30.8)	47.9 (20.1)
40–44 years (n=205)	5	16.7	0.0	37.5	0.0	0.0	0.0	14.6
	10	33.3	12.5	55.0	12.5	0.0	16.7	22.9
	25	41.7	25.0	75.0	37.5	6.3	41.7	35.4
	50	54.2	43.8	87.5	50.0	18.8	66.7	50.0
	75	75.0	62.5	100.0	62.5	37.5	91.7	60.2
	90	91.7	87.5	100.0	75.0	53.7	100.0	74.6
	95	97.1	95.6	100.0	87.5	62.5	100.0	78.1
	Mean (SD)	57.8 (22.5)	45.3 (27.4)	82.6 (21.5)	50.1 (23.4)	23.3 (21.0)	62.6 (30.2)	48.4 (18.4)
45–49 years (n=153)	5	12.5	0.0	25.0	0.0	0.0	0.0	12.3
	10	20.8	0.0	25.0	0.0	0.0	8.3	20.4
	25	33.3	21.9	62.5	37.5	0.0	41.7	29.2
	50	54.2	43.8	75.0	50.0	18.8	58.3	46.4
	75	70.8	62.5	100.0	62.5	31.3	83.3	60.4
	90	91.7	87.5	100.0	75.0	50.0	100.0	72.5
	95	95.8	93.8	100.0	87.5	62.5	100.0	78.1
	Mean (SD)	53.7 (25.2)	42.8 (28.4)	75.4 (26.8)	46.9 (23.9)	20.9 (21.6)	59.4 (29.6)	45.2 (19.8)
50–54 years (n=103)	5	12.9	0.0	37.5	0.0	0.0	0.0	14.7
	10	16.7	0.0	37.5	12.5	0.0	8.3	16.7
	25	37.5	18.8	68.8	37.5	6.3	25.0	28.1
	50	54.2	37.5	87.5	50.0	18.8	50.0	42.7
	75	72.9	62.5	100.0	62.5	31.3	75.0	57.8
	90	87.5	81.3	100.0	75.0	48.7	91.7	67.5
	95	95.4	93.1	100.0	87.5	55.6	100.0	71.8
	Mean (SD)	53.3 (24.5)	40.5 (28.5)	78.8 (24.0)	48.1 (24.0)	20.0 (17.7)	48.0 (30.3)	42.4 (18.8)

(Continues)

TABLE 4 (Continued)

Age group	Percentile	Dimension						
		General well-being	Psychological well-being	Social well-being	Contagiousness	Health	Sexuality	Total score
55–65 years (n=105)	5	13.5	0.0	25.0	3.1	0.0	0.0	12.4
	10	25.0	6.3	25.0	12.5	0.0	0.0	20.3
	25	38.5	31.3	75.0	37.5	12.5	25.0	33.3
	50	62.5	46.9	87.5	50.0	25.0	50.0	47.9
	75	75.0	68.8	100.0	62.5	43.8	83.3	60.9
	90	91.7	87.5	100.0	75.0	68.8	100.0	71.4
	95	95.8	93.8	100.0	100.0	81.3	100.0	79.6
	Mean (SD)	58.2 (25.0)	47.8 (27.2)	78.8 (26.9)	48.6 (23.1)	27.7 (24.0)	52.6 (33.0)	46.8 (19.9)
25–65 years (n=1.352)	5	12.5	0.0	25.0	0.0	0.0	0.0	13.5
	10	20.8	6.3	37.5	12.5	0.0	8.3	19.8
	25	37.5	25.0	75.0	37.5	0.0	33.3	31.3
	50	54.2	43.8	87.5	50.0	18.8	58.3	45.8
	75	75.0	62.5	100.0	62.5	31.3	83.3	59.4
	90	87.5	81.3	100.0	75.0	50.0	100.0	71.4
	95	95.8	93.8	100.0	87.5	68.8	100.0	78.6
	Mean (SD)	55.2 (24.5)	43.7 (27.4)	78.2 (26.0)	47.4 (23.5)	21.8 (21.5)	58.3 (30.9)	45.7 (19.6)

Abbreviation: SD, standard deviation.
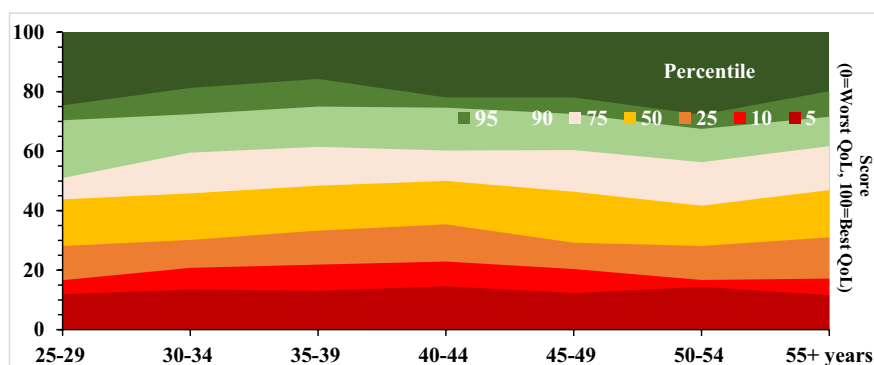
FIGURE 2 Percentiles of the total score of the HPV-QoL scale according to the sample (n:1352). Each percentile indicates the percentage of HPV-QoL scores obtained by women (for the total dimension) that would be expected to fall under that value in the Spanish population. The different values of the percentiles 5, 10, 25, 50, 75, 90, 95, and 100 are represented at the highest HPV-QoL score for each color area and age group, ranging from green (the lowest impact, percentile 100=the best quality of life) to red (the strongest impact, percentile 5=the worst quality of life).
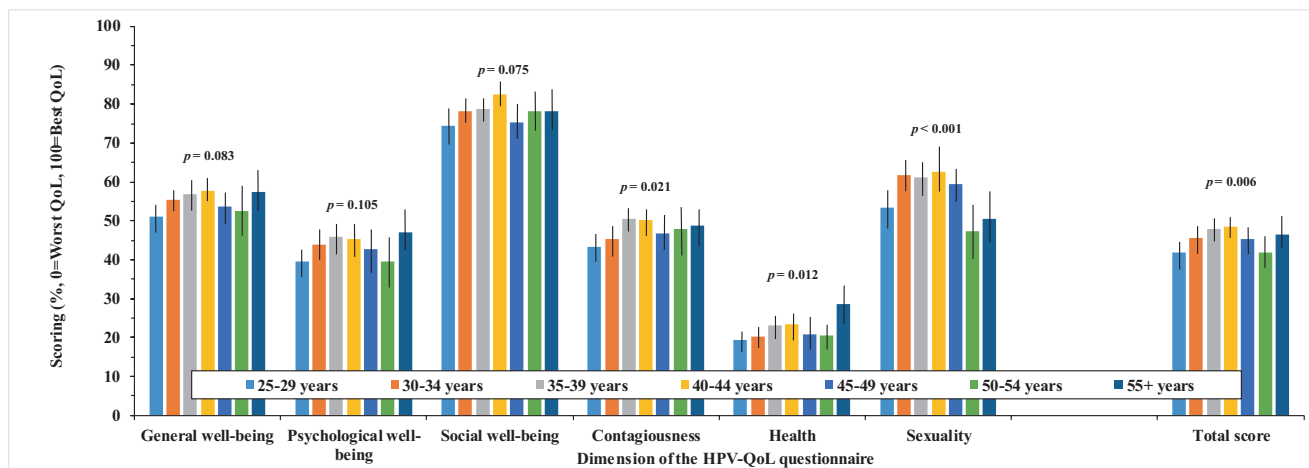
FIGURE 3 Within domain and total score age group comparisons of population-based norms for the HPV-QoL questionnaire.

variables. The age and educational level distribution of the sample closely matched those of the Spanish population. Additionally, the proportions of premenopausal and peri-/postmenopausal women in our sample aligned with the national distribution of women with a history of HPV infection.[32] In addition, the questionnaire collected demographic and medical data from women to create subgroups that could be compared in future studies. Given that comorbidities acting as confounding factors were excluded, we can reasonably conclude that the effects and impairments measured by the HPV-QoL scale were due to the underlying condition (HPV infection). Finally, as HPV vaccination and screening programs become more widespread, the HPV-QoL scale could be used in the following years to evaluate an eventual improvement in the psychological impact of HPV on the QoL due to these health population policies.[33]

This work is not exempt from possible limitations. For instance, the sample size used to calculate population norms can be considered insufficient, particularly within the oldest age stratum (55–65 years), which may have been underrepresented. This could be because the prevalence of HPV infection and the request for assistance in Gynecology are lower in the eldest stratum than in younger strata.[34] Considering that HPV screening in Spain is opportunistic, it is reasonable to conclude that elder women were less likely to be included in our sample.[3] Despite the HPV-QoL questionnaire having been validated for both low- and high-risk HPV genotypes, potential differences in the impact of these genotypes on the QoL were not considered. This might become a limitation, as it has been suggested that QoL impairment is stronger in women with high-risk genotypes.[35] Additionally, the present study did not evaluate possible changes in the impact of HPV between past and active infections, and from the time of the first HPV-positive test. Moreover, the sample was recruited from gynecology clinics, where a higher number of participants with active HPV is expected than women with past HPV. This could be a possible selection bias, as it may not accurately represent the prevalence of HPV in the Spanish population.[15] Studies are ongoing to clarify this aspect further. Another possible limitation is that the sample did not exactly reflect the population density of the different regions in Spain. However, enrolling participants from all Spanish regions is complex, and other similar studies based their nationwide representability on a small number of regions.[16,17,36,37] Thus, we are unable to rule out the possibility of selection bias, which might have interfered with the composition of the Spanish sample in terms of age, socioeconomic level, and educational status, particularly the last factor, since the percentage of women with high-level education (university) enrolled in the study was higher than expected in the Spanish female general population of the same age range.[38] The differences in age composition of the sample could be explained by the fact that HPV-infected women tended to be younger, and this could reduce the Spanish sample in terms of age, socioeconomic level, and educational status. Further studies are required to evaluate the role of HPV in decreasing the QoL. In addition, potential differences between-age groups or Spanish geographical areas and whether HPV infection concerns change after interventions (i.e., surgical or medical) or expectant management should also be studied.

The current population norms were developed for the Spanish population. Consequently, it is not possible to generalize and extend these results and conclusions to other countries. Finally, it must be considered that the present study can only assert a decrease in QoL among women with a history of HPV in Spain. Because this was a cross-sectional study, no causal relationship could be established between HPV infection and worsening QoL.

Several scales have been developed to measure how diseases or infections affect the QoL.[39] The previously mentioned FSFI scale assesses sexual dysfunction that worries or distresses a woman. However, this test was not specifically designed for women with HPV infection. The GHQ-12 and HADS were used to evaluate mental health impairment. The "Functional Assessment of Chronic Illness Therapy-FACIT-CD" scale explores the physical and psychological fields affecting the QoL in patients with cervical dysplasia. Although this scale has been validated for American, Swedish, Serbian, and Brazilian populations, it has only been used in a few studies because it is long and does not focus on HPV infection.[40–43]

Several questionnaires can be used to assess lower genital tract pathologies caused by HPV. The "Cuestionario Específico para Condiloma Acuminado"-CECA questionnaire is an instrument validated for patients with genital warts and it is useful to contrast the QoL in people with these genital lesions compared with the general population.[44] The HPV impact profile (HIP) was developed as a self-administered scale validated for Spanish language.[45] It assesses the psychosocial impact of an abnormal Papanicolaou test result, Cervical Intraepithelial Neoplasia of any grade, and genital warts. The psychometric properties of the HIP scale have also been investigated, showing moderate correlation with other scales, including the HADS, as well as its construct validity.[46] Nonetheless, these scales do not analyze the total spectra of HPV infection impact. In contrast, the HPV-QoL scale is a useful tool to evaluate the impairment in HRQoL in women with HPV, not only because it is specifically designed for this population but also because it allows the detection of vital spheres that are most likely affected by it. To our knowledge, the HPV-QoL is the first scale that focuses on the assessment of HRQoL in women with HPV in which reference population norms have been developed. This would allow the promotion of health initiatives targeted to enhance the fields most responsible for the decrease in HRQoL and detect potential differences in impairment with regard to age and geographical location.

5 | CONCLUSION

Despite the limitations mentioned above, the results support the validity of population-based norms for the novel HPV-QoL questionnaire, which is a valid instrument for measuring the decrease in the QoL among women with HPV in Spain.

AUTHOR CONTRIBUTIONS

All authors contributed substantially to this study. Javier Calvo-Torres, Mar Ramírez-Mena, and Pluvio J. Coronado developed the conceptualization, and Mar Ramírez-Mena, and Pluvio J. Coronado

drafted the methodology. Javier Rejas-Gutiérrez performed the formal statistical analyses. Javier Calvo-Torres, Mar Ramírez-Mena, Pluvio J. Coronado, Javier Rejas-Gutiérrez, Carmen González-Granados, Melissa Bradbury, Marta Del Pino, and Beatriz Procas contributed to writing the (original draft). Javier Calvo-Torres, Mar Ramírez-Mena, Pluvio J. Coronado, and Javier Rejas-Gutiérrez drafted the manuscript (reviewing and editing). All the authors have read and agreed to the published version of the manuscript.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Instituto de Investigación Sanitaria San Carlos (protocol code ISM-220103) on January 3, 2022.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.