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Association of body mass index with anal human papillomavirus infection and histologically confirmed high-grade squamous intraepithelial lesions in people who receive services at the Anal Neoplasia Clinic in Puerto Rico

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ABSTRACT

Objective: This study aimed to assess the association of body mass index (BMI) with anal high-risk human papillomavirus (HR-HPV) and biopsy-confirmed histologic anal high-grade squamous intraepithelial lesions (HSIL) among a clinic-based sample of Hispanics in Puerto Rico.
Methods: This cross-sectional study evaluated medical records of adults who received services at the Anal Neoplasia Clinic of the University of Puerto Rico Comprehensive Cancer Center between October 2014 and December 2022. The study included 543 records with complete clinical information regarding anal HR-HPV and anal HSIL status. Chi-square and logistic regression analyses were performed.
Results: Mean age of participants was 44.10 ± 13.24 years, 65.2% were men, 71.7% were HIV-infected, 74.4% had anal HR-HPV infection, and 37.9% had biopsy-confirmed HSIL. Regarding BMI, 2.4% were underweight, 31.9% normal weight, and 39.0 % overweight; while 17.3 % had class I, 5.2% class II, and 4.2% class III obesity. No significant association was observed between BMI and anal HR-HPV infection in adjusted analyses. Lower odds of anal HSIL were observed among overweight individuals (OR: 0.63, 95% CI: 0.41 – 0.99) and those with class II/III obesity (OR: 0.48, 95% CI: 0.22 – 1.01) compared to adults with underweight/normal BMI, after adjusting for potential confounders. No significant association was observed for class I obesity.
Conclusion: BMI was not associated with anal HR-HPV infection. Overweight and obese individuals had lower odds of having anal HSIL than adults with underweight/normal BMI. This finding could suggest underdiagnosis of HSIL among overweight/obese individuals, or reduced risk in this group.

1. Introduction

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide. (CDC, 2022) In the United States, it is estimated that approximately 14 million people are infected each year. (Siddharthan et al., 2019) In Puerto Rico, the anal HPV prevalence estimate range is 21.5% (14.1% – 31.3%) for women, (Ortiz et al., 2016) and 57.8% (50.5% – 64.9%) for men attending sexually transmitted infections clinics. (Colón-López et al., 2014) Persistent infection with high-risk HPV (HR-HPV) types is a major risk factor for anal cancer. (CDC, 2022; CDC, 2021) Anal HR-HPV infection can cause squamous intraepithelial lesions (SIL), which may be either low-grade squamous intraepithelial lesions (LSIL) or high-grade squamous intraepithelial lesions (HSIL)—the latter are also known as premalignant lesions because they are more likely to progress to anal cancer. (Gaisa et al., 2014; Medina-Laabes et al., 2018; Swedish et al., 2011; Wei et al., 2021) Over 90% of anal cancer cases are caused by a persistent HR-HPV infection, (Leeds, 2016) without treatment, 1.9% of the HSIL cases may progress to cancer. (Palefsky et al., 2022)

There has been a rise in the incidence of anal cancer during the last

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two decades. In the United States, the incidence of anal cancer increased by an average of 2.7% per year from 2001 to 2015. (Deshmukh et al., 2020) In Puerto Rico, the incidence increased even more rapidly: 4.9% per year from 2000 to 2016. (Ortiz-Ortiz et al., 2021) Worldwide, around 25,000 new anal cancer cases were documented in 2008, (Islami et al., 2016) in comparison to more than 50,000 new cases in 2020: (Bruni et al., 2021) more than double in just over 10 years. Risk factors for anal HR-HPV and anal lesions include human immunodeficiency virus (HIV), (Gaisa et al., 2014; Medina-Laabes et al., 2018; Wei et al., 2021; Leeds, 2016; Ortiz-Ortiz et al., 2021) increasing age, (Wei et al., 2021; Olesen et al., 2017) having a high number of sexual partners, (Rosen et al., 2021) cigarette smoking, (Frisch et al., 2022; Keller et al., 2022) sex assigned at birth (usually more common in women than in men), (CDC, 2017) and being a man who has sex with men (MSM). (Wei et al., 2021; Gandra et al., 2015)

Few research studies have evaluated the direct association between body mass index (BMI) and anal HR-HPV infection or anal HSIL, and those that have studied it have yielded inconsistent results. (Olesen et al., 2017; Nyitray et al., 2019; Gunge et al., 2018; Liu et al., 2015; Urbute et al., 2020; Goldstone et al., 2017; Moskowitz and Seal, 2010) Regarding the potential biological plausibility of this association, studies have demonstrated that in women and MSM the number of sexual partners decreases as their BMI increases. (Olesen et al., 2017; Nyitray et al., 2019; Gunge et al., 2018; Liu et al., 2015; Urbute et al., 2020; Goldstone et al., 2017; Moskowitz and Seal, 2010) A lower number of sexual partners might decrease exposure to anal HPV infection and, subsequently, lower the risk of developing anal cancer, which raises the possibility that a higher BMI could be a protective factor. Another study found that people who have been obese for long periods may develop hyperactivated adaptive immunity that keeps latent viruses subdued. (Liu et al., 2015).

Research evaluating the association of BMI with anal HPV infection or anal HSIL in Hispanics is limited or, specifically for Puerto Ricans, nonexistent. This is concerning since the prevalence of obesity in Puerto Rico in 2022 was extremely high, with estimates of 34.1% (95% CI: 32.3% – 35.9%), (CDC, 2022) which represent more than a third of the population. Given the increase in the incidence of anal cancer and the high prevalence of obesity, it is important to evaluate if a high BMI is a risk factor for or a protective factor against anal HR-HPV and/or anal HSIL. Thus, this study assessed the association of BMI with anal HR-HPV infection and anal HSIL among a clinic-based sample of Hispanic adults living in Puerto Rico.

2. Materials and methods

2.1. Design

We performed a cross-sectional study analyzing data from the Anal Neoplasia Clinic of the University of Puerto Rico Comprehensive Cancer Center. This clinic serves people over the age of 18 and is the first in Puerto Rico to specialize in the prevention or treatment of anal SIL. Patients are referred to the clinic if they have had a previous abnormal anal cytology, are at risk for anal cancer because they have other diseases (such as HIV, Crohn's, etc.), or have symptoms that are in any way suggestive of anal cancer. Patients' medical records include socio-demographic factors, medical history, and the results of a physical examination. At the baseline visit, most patients undergo anthropometric measurements, anal HR-HPV testing, and a high-resolution anoscopy (HRA).

For this study, we used information collected during the baseline visit from October 3, 2014, through December 31, 2022 (n = 1193 patients). Of the initial group, 650 individuals were excluded from the analyses because their records were missing the BMI information (n = 157), the anal HR-HPV test results (n = 420), or at least one satisfactory histology test result (n = 70), or they were under 21 years old (n = 3). This left a final study population of 543 individuals (45.5%) who were included in the analysis (Fig. 1).

2.2. Anal HR-HPV screening

The Anal Neoplasia Clinic's anal HR-HPV test consists of inserting a Dacron swab about 4 cm into the anal canal and rotating it 360° over the walls of the anal canal for no more than 30 s to obtain cellular tissue. The swab is then inserted into a collection tube ThinPrep PreservCyt solution to deposit the sample cells obtained. The sample is sent to the laboratory for a Cobas 4800 test, which detects HPV-16, HPV-18, and 12 other HR-HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). (Ramos-Cartagena et al., 2020)

2.3. High-resolution anoscopy (HRA)

The procedure is initiated by inserting an anoscope into the anus. The obturator of the anoscope is removed and replaced with a gauze-wrapped swab soaked in 3% acetic acid. After approximately 2 min, the anoscope, gauze, and swab are also removed. The anoscope is then placed back into the anus and more acetic acid is applied to distinguish abnormal epithelial cells. Next, Lugol's iodine stain is applied, which creates a contrast between healthy and unhealthy anal cells. The physician who performs the test takes a sample of any tissue that appears abnormal and sends it to a histopathology laboratory to be classified as benign, LSIL, HSIL, cancerous, or unsatisfactory (it was not possible to analyze it). (Keller et al., 2022; Ramos-Cartagena et al., 2020)

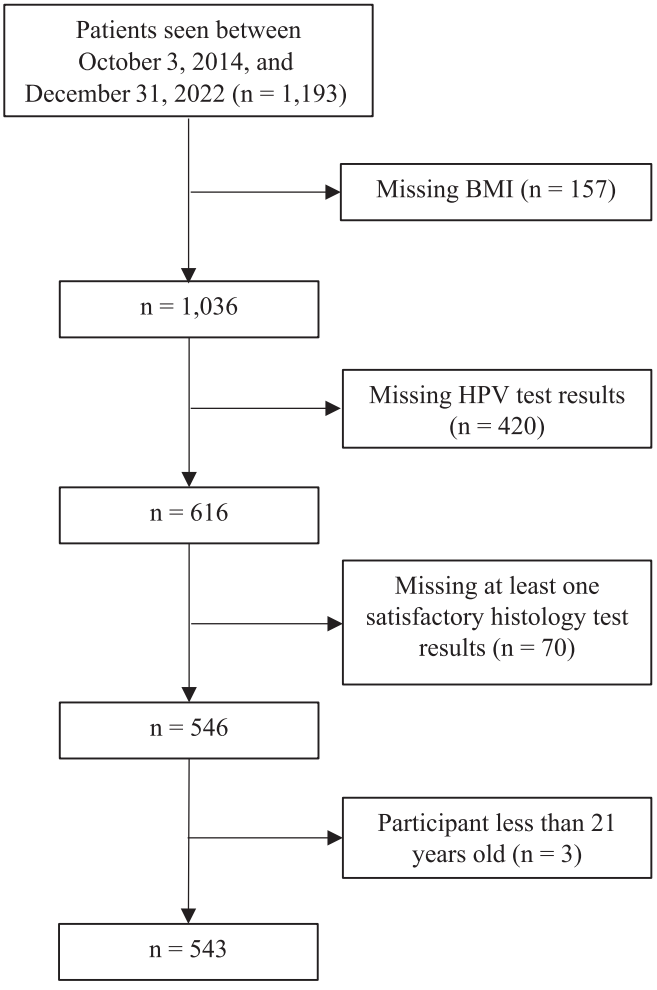

Fig. 1. Flow chart of study sample and exclusion criteria.

2.4. Database

All sociodemographic and clinical data is extracted from the medical records and entered to the REDCap platform without any personal identifiers. This study was approved by the University of Puerto Rico, Medical Science Campus Institutional Review Board (IRB #: 2211059154). The study followed the guidelines for the protection of human subjects to ensure the safety and privacy of study participants.

2.5. Statistical analysis

Descriptive statistics were used to describe the sociodemographic, behavioral, and clinical characteristics of the study sample when they visited the clinic. Percentages and frequencies were used to explain categorical variables and mean and standard deviations (SD) were used for continuous variables. Anal HR-HPV status was defined as positive if the patient was positive for at least one HR-HPV type and negative if the person was negative for all HR-HPV types screened for by the Cobas test. The histological results were categorized as no HSIL (including benign SIL and LSIL [condyloma, AIN-1, or AIN-2 negative for p16]) and HSIL (AIN-2 positive for p16 or AIN-3). (Darragh et al., 2012) BMI was analyzed as a categorical variable as follows: underweight (<18.5 kg/m^2), normal weight (18.5 kg/m^2–24.9 kg/m^2), overweight (25.0 kg/m^2 – 29.9 kg/m^2), class I obesity (30.0 kg/m^2– 34.9 kg/m^2), class II obesity (35.0 kg/m^2– 39.9 kg/m^2) or class III obesity (≥40.0 kg/m^2). (Bethesda, 1998; Jensen et al., 2013) Additional variables considered were sex assigned at birth (male or female), HIV status (positive or negative), age in years, current smoking status (yes or no), lifetime number of sexual partners (1–10 or 11+), number of sexual partners in the last 12 months (0–10 or 11+), receptive anal intercourse in the last 12 months (yes or no), and lifetime receptive anal intercourse (yes or no).

Bivariate analyses were performed using Pearson's chi-square statistic or Fisher's test, as appropriate. We used crude and adjusted logistic regression models to measure associations between the covariates. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using the generalized linear model method. Results with p-values < 0.05 were considered statistically significant (identified in bold). To study the associations between BMI and the main variables of interest 1) anal HR-HPV status; and 2) anal HSIL, the likelihood ratio test was used to assess interaction terms. Different models were constructed, adjusting for variables of relevance in the literature and evaluating model fit. Stepwise regression was also used to select predictive variables to include in the models: variables with a significance of 0.10 for addition and 0.15 for subtraction were used. Model fit was assessed with the Akaike information criterion (AIC), the smaller the value the better. (Akaike, 1974) All the analyses were performed using RStudio (ver. 2022.07.2 + 576) and Stata (ver. 17).

3. Results

Of the 543 individuals in the study, 65.2% were men (sex assigned at birth), the mean age was 44.10 years ± 13.24 SD, and 71.7% were HIV positive. Regarding lifestyles, 22.7% were current smokers in the baseline visit, 48.2% had 11+ lifetime sexual partners, and 9.8% had 11+ sexual partners in the last 12 months. In addition, 67.3% had receptive anal intercourse during their lifetimes and 43.7% had receptive anal intercourse in the last 12 months. As for BMI, 39.0% of participants were overweight and 26.7% were obese. Finally, 74.4% were positive for HR-HPV in the anus and 37.9% had anal HSIL according to their histologic results (Table 1).

The prevalence of anal HR-HPV infection was higher in people aged ≤44 years, individuals who were HIV-positive compared with those who were HIV-negative, current smokers, people who had 11 or more lifetime sexual partners, and those who reported lifetime receptive anal intercourse and in the past 12 months ($p < 0.05$). We observed statistically significant associations between HSIL and each of the following variables: HIV status, lifetime receptive anal intercourse, and receptive anal intercourse in the last 12 months ($p < 0.05$) (Table 2).

Given the low number of underweight individuals in our sample, the underweight and normal BMI categories were merged. For similar reasons, we also combined individuals with class II and III obesity. We observed statistically significant associations between BMI and each of the following variables: sex assigned at birth, age, receptive anal intercourse (lifetime), and anal HR-HPV infection (Table 3). More specifically, the prevalence of BMI classified as underweight/normal and overweight was higher in males than in females (37.9% vs. 27.5%, and 42.4% vs. 32.8%, respectively [$p < 0.001$]). On the other hand, the prevalence of class I and class II/III obesity was higher in females than in males (21.7% vs. 15.0% and 18.0% vs. 4.8%, respectively [$p < 0.001$]).

Table 1
Sociodemographic, behavioral, and clinical characteristics of a clinic-based sample of adults from the Anal Neoplasia Clinic in San Juan, Puerto Rico (n = 543).

Characteristic	n (%)
Age, years	
Mean (±SD)	44.10 (±13.24)
≤44	274 (50.5)
45+	269 (49.5)
Sex assigned at birth	
Female	189 (34.8)
Male	354 (65.2)
HIV status[a]	
Negative	153 (28.3)
Positive	388 (71.7)
BMI	
Underweight	13 (2.4)
Normal	173 (31.9)
Overweight	212 (39.0)
Class I Obesity	94 (17.3)
Class II Obesity	28 (5.2)
Class III Obesity	23 (4.2)
Current smoking status[b]	
No	409 (77.3)
Yes	120 (22.7)
Number of sexual partners (lifetime)[c]	
1–10 partners	270 (51.8)
11+ partners	251 (48.2)
Number of sexual partners (last 12 months)[d]	
0–10 partners	367 (90.2)
11+ partners	40 (9.8)
Receptive anal intercourse (lifetime)[e]	
No	168 (32.7)
Yes	346 (67.3)
Receptive anal intercourse (last 12 months)[f]	
No	254 (56.3)
Yes	197 (43.7)
HR-HPV infection[+]	
Negative	139 (25.6)
Positive	404 (74.4)
HSIL	
No	337 (62.1)
Yes	206 (37.9)

Missing values: [a]n = 2 | [b]n = 14 | [c]n = 22 | [d]n = 136 | [e]n = 29 | [f]n = 92. [+]Types of HR-HPV: 16, 18 and/or other (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and/or 68).

Table 2
Factors associated with anal HR-HPV infection and anal HSIL among adults from the Anal Neoplasia Clinic in San Juan, Puerto Rico (n = 543). Bold values indicates statistically significant (p-value < 0.05).

Variable	HR-HPV			HSIL		
	No n (%)	Yes n (%)	p-value	No n (%)	Yes n (%)	p-value
Sex assigned at birth						
Female	54 (28.6)	135 (71.4)	0.291	128 (67.7)	61 (32.3)	0.058
Male	85 (24.0)	269 (76.0)		209 (59.0)	145 (41.0)	
Age (years)						
≤44	57 (20.8)	217 (79.2)	**0.013**	168 (61.3)	106 (38.7)	0.784
45+	82 (30.5)	187 (69.5)		169 (62.8)	100 (37.2)	
HIV status[a]						
Negative	58 (37.9)	95 (62.1)	**<0.001**	107 (69.9)	46 (30.1)	**0.021**
Positive	81 (20.9)	307 (79.1)		228 (58.8)	160 (41.2)	
Current smoking status[b]						
No	118 (28.9)	291 (71.1)	0.011	266 (65.0)	143 (35.0)	0.110
Yes	20 (16.7)	100 (83.3)		62 (51.7)	58 (48.3)	
Number of sexual partners (lifetime)[c]						
1–10 partners	78 (28.9)	192 (71.1)	**0.040**	178 (65.9)	92 (34.1)	0.083
11+ partners	52 (20.7)	199 (79.3)		146 (58.2)	105 (41.8)	
Number of sexual partners (last 12 months)[d]						
0–10 partners	103 (28.1)	264 (71.9)	0.215	227 (61.9)	140 (38.1)	0.327
11+ partners	7 (17.5)	33 (82.5)		21 (52.5)	19 (47.5)	
Receptive anal intercourse (lifetime)[e]						
No	67 (39.9)	101 (60.1)	**<0.001**	122 (72.6)	46 (27.4)	**0.001**
Yes	67 (19.4)	279 (80.6)		196 (56.6)	150 (43.4)	
Receptive anal intercourse (last 12 months) [f]						
No	83 (32.7)	171 (67.3)	**0.003**	174 (68.5)	80 (31.5)	**0.006**
Yes	39 (19.8)	158 (80.2)		109 (55.3)	88 (44.7)	

Missing values: [a]n = 2 | [b]n = 14 | [c]n = 22 | [d]n = 136 | [e]n = 29| [f]n = 92.

Differences were also observed by age: older individuals were more likely to be overweight or obese (p = 0.006). In addition, for all classes of obesity, it was less frequent to have 11+ lifetime sexual partners (p = 0.069) and receptive anal intercourse (lifetime) (p = 0.032). Regarding differences by anal HR-HPV status, while 13.7% of HR-HPV-negative individuals had class II/III obesity, only 7.9% of those who were positive for anal HR-HPV were in this BMI category (p = 0.045).

In the crude analysis, the logistic regression model showed that people with class II/III obesity had decreased odds of anal HR-HPV infection than individuals with a BMI that was underweight/normal (OR = 0.48, 95% CI: 0.25 – 0.94). No significant differences were observed between the overweight or class I obesity groups and the underweight/normal weight group.

Due to numerous missing values for some of the covariables (e.g.,

Table 3
Factors associated with BMI among adults from the Anal Neoplasia Clinic in San Juan, Puerto Rico (n = 543). Bold values indicates statistically significant (p-value < 0.05).

Variables	BMI				
	Underweight/ Normal n (%)	Overweight n (%)	Class I Obesity n (%)	Class II & III Obesity n (%)	p-value
Sex at birth					
Female	52 (27.5)	62 (32.8)	41 (21.7)	34 (18.0)	**<0.001**
Male	134 (37.9)	150 (42.4)	53 (15.0)	17 (4.8)	
Age (years)					
≤44	113 (41.2)	96 (35.0)	44 (16.1)	21 (7.7)	**0.006**
45+	73 (27.1)	116 (43.1)	50 (18.6)	30 (11.2)	
HIV status[a]					
Negative	45 (29.4)	69 (45.1)	25 (16.3)	14 (9.2)	0.307
Positive	140 (36.1)	142 (36.6)	69 (17.8)	37 (9.5)	
Current smoking status[b]					
No	137 (33.5)	164 (40.1)	70 (17.1)	38 (9.3)	0.845
Yes	43 (35.8)	43 (35.8)	21 (17.5)	13 (10.8)	
Number of sexual partners (lifetime)[c]					
1–10 partners	86 (31.9)	103 (38.2)	47 (17.4)	34 (12.6)	0.069
11+ partners	91 (36.3)	103 (41.0)	42 (16.7)	15 (6.0)	
Number of sexual partners (last 12 months)[d]					
0–10 partners	121 (33.0)	149 (40.6)	59 (16.1)	38 (10.4)	0.129[※]
11+ partners	15 (37.5)	18 (45.0)	7 (17.5)	0 (0.00)	
Receptive anal intercourse (lifetime)[e]					
No	49 (29.2)	63 (37.5)	32 (19.1)	24 (14.3)	**0.032**
Yes	125 (36.1)	142 (41.0)	54 (15.6)	25 (7.2)	
Receptive anal intercourse (last 12 months)[f]					
No	77 (30.3)	99 (39.0)	46 (18.1)	32 (12.6)	0.054
Yes	70 (35.5)	87 (44.2)	28 (14.2)	12 (6.1)	
Anal HR-HPV infection[+]					
Negative	41 (29.5)	61 (43.9)	18 (12.9)	19 (13.7)	**0.045**
Positive	145 (35.9)	151 (37.4)	76 (18.8)	32 (7.9)	
Anal HSIL					
No	106 (31.5)	138 (40.9)	55 (16.3)	38 (11.3)	0.081
Yes	80 (38.8)	74 (35.9)	39 (18.9)	13 (6.3)	

Missing values: [a]n = 2 | [b]n = 14 | [c]n = 22 | [d]n = 136 | [e]n = 29| [f]n = 92. [※]Fisher test was used. [+] Types of HR-HPV: 16,18 and/or other (31, 33, 35, 39, 45, 51, 52, 58, 59, 66, and/or 68).

sexual behavior in the last 12 months), for the adjusted regression models we only considered sex assigned at birth, HIV status, age, current smoking status, lifetime number of sexual partners, and lifetime history of receptive anal intercourse. In the first multivariate logistic regression model for HR-HPV (Model 1, Table 4), individuals with class II/III obesity were less likely to have anal HR-HPV infection; this result was marginally significant (OR = 0.52. 95% CI: 0.26 – 1.08). While results were not significant in the other two adjusted models (Model 2 and Model 3), results showed similar OR values, with slightly more variability.

For anal HSIL, the crude analysis showed that overweight individuals (OR = 0.71, 95% CI: 0.47 – 1.06) and those with class II/III obesity (OR = 0.45, 95% CI: 0.22 – 0.89) were less likely to have anal HSIL than individuals classified as underweight/normal weight. Although not statistically significant, there was a decrease in the odds of anal HSIL in individuals with class I obesity compared with the underweight/normal weight group (OR = 0.94, 95% CI: 0.57 – 1.55). A similar pattern was observed in Model 1 (adjusted for sex assigned at birth, age, and lifetime history of receptive anal intercourse), where overweight individuals (OR = 0.61, 95% CI: 0.39 – 0.93) and those with class II/II obesity (OR = 0.45, 95% CI: 0.21 – 0.92) had reduced odds of anal HSIL. No statistically significant difference was observed between individuals with class I obesity compared to those classified as underweight/normal BMI. The other two adjusted models resulted in quite similar OR's and CI values (Table 5).

4. Discussion

To our knowledge, this is one of the first studies conducted among Hispanics and in Puerto Rico evaluating the association of BMI with anal HR-HPV and anal HSIL. Almost two-thirds of the study population (65.7%) were overweight or obese. In addition, there was a high prevalence of anal HR-HPV (74.4%) and anal HSIL (37.9%). Overall, 46% of study participants came referred to the clinic because of an abnormal anal cytology (data not shown), which could influence the observed high prevalence of anal HPV and HSIL. Despite this, results showed that this is a population at high risk of anal cancer and metabolic disorders.

In all models, people with a BMI classified as overweight or class II/III obesity had lower odds of being positive for anal HR-HPV in comparison to people with an underweight/normal BMI. This result was statistically significant for people with class II/III obesity in the crude model (OR 0.48, 95% CI: 0.25 – 0.94) and marginally significant when adjusting for relevantcovariates (OR 0.52, 95% CI: 0.26 – 1.08, Model 1), including certain sexual practices. A possible explanation is that people with high BMI have higher concentrations of several cytokines, including tumor necrosis factor-α and interleukin-6; this elevation in innate immune response may translate into an effective defense against viral pathogens, including HPV. Thus, people who have been obese for a long time may have developed a hyperactivated adaptive immunity that keeps latent viruses at bay compared with people with a normal BMI. (Liu et al., 2015) Another explanation could be that performing anal cancer screening is more challenging in people with higher BMI than in those with normal BMI. This could lead to anal HPV being underdiagnosed in this population. Similar results were reported in a study among women (n = 944,227), where cervical HPV prevalence decreased as BMI increased, but increased cervical cancer risk was observed among overweight and obese patients (Clarke et al., 2018). In addition, lower sensitivity for cervical HPV testing and cytology was reported in this study among overweight and obese women, which resulted in the underdiagnosis of HPV and precancer. (Clarke et al., 2018).

In the case of people with class I obesity, all models showed that they had higher odds of being positive for anal HR-HPV types than individuals with an underweight/normal BMI, although this finding was not statistically significant. Overweight and obese individuals showed lower odds of HSIL in comparison with those with an underweight/normal BMI. Results were significant or marginally significant for overweight and obese individuals in all the models evaluated, but not for individuals with class I obesity. The reduced odds of anal HSIL among overweight and obese individuals could potentially be explained by difficulties in the ability to detect lesions among individuals with higher BMI during the HRA procedure. In cervical cancer screening, it has been found that when colposcopy is performed, sampling, visualization, and taking biopsies in women with higher BMI is more challenging compared with doing the procedure on women with normal BMI. (Graham et al., 2022; Clarke et al., 2020) Given the high prevalence of obesity in Puerto Rico and the United States, (CDC, 2022) it is important to highlight the need for adequate screening tools for this population.

According to the consensus guidelines, created by the International Anal Neoplasia Society (IANS), anal cancer screening is recommended for MSM and transgender women with HIV starting at 35 years and for women and men who have sex with women with HIV starting at 45 years (Stier et al., 2024). These recommendations highlight the importance of developing research studies that evaluate the sensitivity and specificity

Table 4
Logistics regression models of the association of BMI with anal HR-HPV among adults from the Anal Neoplasia Clinic in San Juan, Puerto Rico. Bold values indicates statistically significant (p-value < 0.05).

Levels	OR_{crude} (95% CI)	$OR_{Model\ 1}$ (95% CI)	$OR_{Model\ 2}$ (95% CI)	$OR_{Model\ 3}$ (95% CI)
Underweight/ Normal	1.00	1.00	1.00	1.00
Overweight	0.70 (0.44 – 1.10)	0.71 (0.44 – 1.15)	0.76 (0.46 – 1.25)	0.79 (0.47 – 1.31)
Class I Obesity	1.19 (0.65 – 2.26)	1.28 (0.67 – 2.53)	1.52 (0.78 – 3.09)	1.51 (0.76 – 3.15)
Class II/III Obesity	**0.48 (0.25 – 0.94)**	0.52 (0.26 – 1.08)*	0.57 (0.28 – 1.17)	0.63 (0.30 – 1.35)

Model description:
Crude: n = 543; R^2 = 0.015; AIC = 617.82.
Model 1: Adjusted for sex assigned at birth, age, and lifetime receptive anal intercourse. n = 514; R^2 = 0.065; AIC = 570.59.
Model 2 (Stepwise recommendation): Adjusted for HIV status, age, current smoking status, and lifetime receptive anal intercourse. n = 501; R^2 = 0.099; AIC = 545.97.
Model 3 (Model with better AIC): Adjusted for sex assigned at birth, HIV status, age, current smoking status, lifetime sexual partners, and lifetime receptive anal intercourse. n = 484; R^2 = 0.094; AIC = 527.65.
*p-value ≥ 0.05 and ≤ 0.10.

Table 5
Logistics regression models of the association of BMI with anal HSIL among adults from the Anal Neoplasia Clinic in San Juan, Puerto Rico.

Levels	OR_{crude} (95% CI)	$OR_{Model\ 1}$ (95% CI)	$OR_{Model\ 2}$ (95% CI)	$OR_{Model\ 3}$ (95% CI)
Underweight/ Normal	1.00	1.00	1.00	1.00
Overweight	0.71 (0.47 – 1.06)*	**0.61 (0.39 – 0.93)**	**0.59 (0.39 – 0.91)**	**0.63 (0.41 – 0.99)**
Class I Obesity	0.94 (0.57 – 1.55)	0.77 (0.45 – 1.32)	0.72 (0.41 – 1.24)	0.76 (0.43 – 1.33)
Class II/III Obesity	**0.45 (0.22 – 0.89)**	**0.45 (0.21 – 0.92)**	**0.40 (0.19 – 0.81)**	0.48 (0.22 – 1.01)*

Model descriptions:
Crude: n = 543; R^2 = 0.012; AIC = 721.95.
Model 1: Adjusted for sex assigned at birth, age, and lifetime receptive anal intercourse. n = 514; R^2 = 0.043; AIC = 674.95.
Model 2 (Stepwise recommendation): Adjusted for HIV status, current smoking status and lifetime receptive anal intercourse. n = 501; R^2 = 0.060; AIC = 650.20.
Model 3 (Model with better AIC): Adjusted for sex assigned at birth, HIV status, age, current smoking status, lifetime sexual partners, and lifetime receptive anal intercourse. n = 484; R^2 = 0.065; AIC = 630.59.
*p-value ≥ 0.05 and ≤ 0.10.

of anal cancer screening tools among people with higher BMI. A limitation of the study was that it was not possible to use the variables "number of sexual partners" and "receptive anal intercourse" (both in the last 12 months) for the regression models due to the high number of missing values (n = 136 and n = 92, respectively). Thus, given that models could not be adjusted for recent sexual behavior, residual confounding of sexual behaviors may be present. In addition, because this was a cross-sectional study, all variables were collected at the same time; therefore, it was not possible to establish causality. In addition, information on the history of obesity across the life course was not available. Other limitations could include recall bias in the reporting of sexual history or hesitancy to reveal the actual number of sexual partners during the medical interview. Moreover, the clinic is located in San Juan, Puerto Rico, which could result in a lower representation of patients from municipalities further away. The clinic is also a referral center for patients with abnormal anal cytology, which may result in an overrepresentation of individuals with anal HR-HPV infection and anal HSIL. Despite these limitations, the biggest strength of this study is that the main study variables (BMI, anal HR-HPV, and anal HSIL) were assessed through clinical procedures. Another strength is that anal HSILs were histologically confirmed by biopsy during the HRA performed by trained physicians.

5. Conclusion

While this study did not show a consistent association between BMI with anal HR-HPV infection and HSIL, overweight and obese individuals had lower odds to have anal HSIL as compared with underweight/normal BMI adults. This finding could suggest underdiagnosis of HSIL among overweight/obese individuals or reduced risk in this group. Given increasing trends of obesity and anal cancer, as well as the lack of standardized guidelines for HSIL screening and treatment in the United States, it is important to continue to understand the factors that may place individuals at risk. It is recommended that future longitudinal studies evaluate waist-to-hip ratio, in addition to BMI, as another anthropometric and metabolic measure, to evaluate if different results are obtained. Also, self-administered questionnaires for sexual practices should be considered, to avoid missing or misrepresented data during the medical interview. While models were adjusted for sexual practices, differences in sexual activity by weight status and the impact of these differences should be explored further.

CRediT authorship contribution statement

Kehvyn Cedeño: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Claudia P. Amaya-Ardila:** Writing – review & editing, Validation, Methodology, Formal analysis. **Jeslie M. Ramos-Cartagena:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Humberto M. Guiot:** Writing – review & editing, Resources, Investigation, Conceptualization. **Cristina Muñoz:** Resources, Project administration, Investigation. **Maribel Tirado-Gómez:** Supervision, Investigation, Funding acquisition. **Ana P. Ortíz:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Dr. Ortiz participates in an institutional grant funded by Merck.

Data availability

The analyses were performed with a clinic database, but the information, without identifiers, was kept for research purposes.

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Ethics

The University of Puerto Rico, Medical Science Campus Institutional Review Board granted ethical approval for this study (IRB #: 2211059154).

References

Akaike, H., 1974. A new look at the statistical model identification. IEEE Trans Automat Contr. 19 (6), 716–723.

Bethesda, M., 1998. Executive Summary of the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report [Internet]. National Heart, Lung, and Blood Institute; 1998 [cited 2022 Jul 14]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2003/.

Bruni, L., Albero, G., Serrano, B., Mena, M., Collado, J., Gómez, D., et al. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in the World. Summary Report 22 October 2021.; 2021.

CDC, 2017. Prevalence of HPV in Adults Aged 18–69: United States, 2011–2014 [Internet]. 2017 [cited 2022 Jul 3]. Available from: https://www.cdc.gov/nchs/products/databriefs/db280.htm.

CDC, 2021. HPV and Cancer [Internet]. 2021 [cited 2022 Jul 3]. Available from: https://www.cdc.gov/cancer/hpv/statistics/cases.htm#:~:text=For%20example%2C%20about%207%2C334%20people,shown%20in%20the%20table%20below.

CDC, 2022. Genital HPV Infection – Basic Fact Sheet [Internet]. 2022 [cited 2022 Jul 3]. Available from: https://www.cdc.gov/std/hpv/stdfact-hpv.htm#:~:text=What%20is%20HPV%3F,many%20different%20types%20of%20HPV.

CDC, 2022. Adult Obesity Maps [Internet]. 2022 [cited 2023 Sep 21]. Available from: https://www.cdc.gov/obesity/data/prevalence-maps.html#overall.

Clarke, M.A., Fetterman, B., Cheung, L.C., Wentzensen, N., Gage, J.C., Katki, H.A., et al., 2018. Epidemiologic evidence that excess body weight increases risk of cervical cancer by decreased detection of precancer. J. Clin. Oncol. [internet]. Apr 4 [cited 2024 May 30];36(12):1184. Available from: /pmc/articles/PMC5908221/.

Clarke, M.A., Massad, L.S., Khan, M.J., Smith, K.M., Guido, R.S., Mayeaux, E., et al., 2020. Challenges associated with cervical cancer screening and management in obese women. J. Low Genit Tract. Dis. 24 (2), 184–191.

Colón-López, V., Ortiz, A.P., Del Toro-Mejías, L., Clatts, M.C., Palefsky, J.M., 2024. Epidemiology of Anal HPV Infection in High-Risk Men Attending a Sexually Transmitted Infection Clinic in Puerto Rico. PLoS One [Internet]. 2014 Jan 6 [cited 2022 Dec 18];9(1):83209. Available from: /pmc/articles/PMC3882217/.

Darragh, T.M., Colgan, T.J., Cox, J.T., Heller, D.S., Henry, M.R., Luff, R.D., et al., 2012. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the college of American Pathologists and the American Society for Colposcopy and Cervical Pathology. Available from: Arch. Pathol. Lab Med. [internet]. 136 (10), 1266–1297 https://meridian.allenpress.com/aplm/article/136/10/1266/133088/The-Lower-Anogenital-Squamous-Terminology.

Deshmukh, A.A., Suk, R., Shiels, M.S., Sonawane, K., Nyitray, A.G., Liu, Y., et al., 2020. Recent trends in squamous cell carcinoma of the anus incidence and mortality in the United States, 2001–2015. Available from: JNCI: J. Natl. Cancer Inst. [internet]. 112 (8), 829–838 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7825484/.

Frisch M, Glimelius B, Wohlfahrt J, Adami HO, Melbye M. Tobacco Smoking as a Risk Factor in Anal Carcinoma: an Antiestrogenic Mechanism? [cited 2022 Jul 14]; Available from: https://academic.oup.com/jnci/article/91/8/708/2519420.

Gaisa, M., Sigel, K., Hand, J., Goldstone, S., 2014. High rates of anal dysplasia in HIV-infected men who have sex with men, women, and heterosexual men. AIDS 28 (2), 215–222.

Gandra, S., Azar, A., Wessolossky, M., 2015. Anal high-risk human papillomavirus infection and high-grade anal intraepithelial neoplasia detected in women and heterosexual men infected with human immunodeficiency virus. HIV/AIDS - Research and Palliative Care.

Goldstone, R.N., Hasan, S.R., Drury, S., Darragh, T.M., van Zante, A., Goldstone, S.E., 2017 Mar 21. A trial of radiofrequency ablation for anal intraepithelial neoplasia. Int J Colorectal Dis. 32 (3), 357–365.

Graham, Y., Hayes, C., Cox, J., Mahawar, K., Fox, A., Yemm, H., 2022. A systematic review of obesity as a barrier to accessing cancer screening services. Available from: Obes. Sci. Pract. [internet] 8 (6), 715–727 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9722456/.

Gunge, V.B., Juul, K.E., van den Brule, A.J.C., Iftner, T., Kjær, S.K., 2018. Sexual inactivity and occurrence of STIs in relation to weight status in women: Two large population-based studies. Women Health 58 (7), 790–805.

Islami, F., Ferlay, J., Lortet-Tieulent, J., Bray, F., Jemal, A., 2016. International trends in anal cancer incidence rates. Int. J. Epidemiol., dyw276

Jensen M, Ryan D, Donato K, Apovian C, Ard J, Comuzzie A, et al. Managing overweight and obesity in adults: systematic evidence review from the obesity expert panel, 2013. S2 ed. Vol. 22. 2013.

Keller, K., Ramos-Cartagena, J.M., Guiot, H.M., Muñoz, C., Rodríguez, Y., Colón-López, V., et al., 2022. Association of smoking with anal high-risk HPV infection and histologically confirmed anal high-grade squamous intraepithelial lesions among a clinic-based population in Puerto Rico. Cancer Treat Res. Commun. 30, 100503.

Leeds, I.L., 2016. Anal cancer and intraepithelial neoplasia screening: A review. World J. Gastrointest Surg. 8 (1), 41.

Liu, S.H., Chen, H.J., Hsieh, T.H., Chen, J.C., Huang, Y.C., 2015. Excessive adiposity, metabolic health, and risks for genital human papillomavirus infection in adult women: a population-based cross-sectional study. BMC Obes. 2 (1), 39.

Medina-Laabes, D.T., Suarez-Perez, E.L., Guiot, H.M., Muñoz, C., Colón-López, V., Tirado-Gómez, M., et al., 2018 Oct. Human papillomavirus correlates with histologic anal high-grade squamous intraepithelial lesions in hispanics with HIV. J Low Genit Tract Dis. 22 (4), 320–325.

Moskowitz, D.A., Seal, D.W., 2010 Jun 21. Revisiting obesity and condom use in men who have sex with men. Arch. Sex Behav. 39 (3), 761–765.

Nyitray, A.G., Peng, F., Day, R.S., Carvalho Da Silva, R.J., Baggio, M.L., Salmerón, J., et al., 2019. The association between body mass index and anal canal human papillomavirus prevalence and persistence: the HIM study. Hum. Vaccin. Immunother. 15 (7–8), 1911–1919.

Olesen, T.B., Mwaiselage, J., Iftner, T., Kahesa, C., Rasch, V., Frederiksen, K., et al., 2017. Risk factors for genital human papillomavirus among men in Tanzania. J Med Virol. 89 (2), 345–351.

Ortiz, A.P., Romaguera, J., Pérez, C.M., González, D., Muñoz, C., González, L., et al., 2016. Prevalence, genotyping, and correlates of anogenital HPV infection in a population-based sample of women in Puerto Rico. Papillomavirus Res. [internet]. Dec 1 [cited 2022 Dec 18];2: 89 . Available from: /pmc/articles/PMC5886867/.

Ortiz-Ortiz KJ, Ramos-Cartagena JM, Deshmukh AA, Torres-Cintrón CR, Colón-López V, Ortiz AP. Squamous Cell Carcinoma of the Anus Incidence, Mortality, and Survival Among the General Population and Persons Living With HIV in Puerto Rico, 2000-2016. JCO Glob Oncol [Internet]. 2021 Dec [cited 2022 Aug 17];(7):133–43. Available from: https://ascopubs.org/doi/full/10.1200/GO.20.00299.

Palefsky JM, Lee JY, Jay N, Goldstone SE, Darragh TM, Dunlevy HA, et al. Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer. New England Journal of Medicine [Internet]. 2022 Jun 16 [cited 2024 Jun 4];386(24): 2273–82. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2201048.

Ramos-Cartagena, J.M., Pérez, C.M., Guiot, H.M., Amaya-Ardilla, C.P., Tirado-Gómez, M., Ortiz, A.P., 2020 Jan. Assessment of anal cancer screening tools in detecting high-grade anal squamous intraepithelial lesions in women. J. Low Genit. Tract Dis. 24 (1), 75–81.

Rosen, B.L., Gorbach, P., Ding, L., Covert, C., Ermel, A.C., Chandler, E., et al., 2021. Sexual network patterns and their association with genital and anal human papillomavirus infection in adolescent and young men. J. Adolescent Health. 68 (4), 696–704.

Siddharthan V. R, Lanciault C, Tsikitis VL. Anal intraepithelial neoplasia: diagnosis, screening, and treatment. Ann Gastroenterol [Internet]. 2019 Feb 18 [cited 2023 Mar 27];32(3):257–63. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6479653/.

Stier, E.A., Clarke, M.A., Deshmukh, A.A., Wentzensen, N., Liu, Y., Poynten, I.M., et al., 2024. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. Available from: Int. J. Cancer [internet]. 154 (10), 1694–1702 https://onlinelibrary.wiley.com/doi/full/10.1002/ijc.34850.

Swedish, K.A., Lee, E.Q., Goldstone, S.E., 2011 Aug. The changing picture of high-grade anal intraepithelial neoplasia in men who have sex with men: the effects of 10 years of experience performing high-resolution anoscopy. Dis Colon Rectum. 54 (8), 1003–1007.

Urbute, A., Thomsen, L.T., Belmonte, F., Kesmodel, U.S., Frederiksen, K., Kjaer, S.K., 2020 Sep. The role of body mass index in incidence and persistence of cervical human papillomavirus infection. Ann Epidemiol. 49, 36–41.

Wei, F., Gaisa, M.M., D'Souza, G., Xia, N., Giuliano, A.R., Hawes, S.E., et al., 2021. Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies. Lancet HIV. 8 (9), e531–e543.