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HPV vaccine uptake among overweight and obese US adolescents: An analysis of the National Health and Nutrition Examination Survey (NHANES) 2009–2014

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ABSTRACT

Background: Human papillomavirus (HPV) vaccine uptake in the US is suboptimal; identifying risk factors associated with low vaccine uptake is critical to increase vaccination coverage. Some evidence suggests body mass index (BMI) is associated with low HPV vaccine uptake and increased risk of HPV infection in adults. BMI may therefore be an important factor in targeting HPV vaccine to US adolescents.
Methods: We investigated the relationship between BMI categories (underweight, normal weight, overweight and obese) and HPV vaccine uptake in 4109 adolescents (9–18 years old) using data from the 2009 to 2014 National Health and Nutrition Examination Survey (NHANES). We used modified Poisson regression to assess the relationship between BMI and receipt of at least one HPV vaccine, and BMI and completion of the vaccine three-dose series. We assessed the relationship between BMI and age at first HPV vaccination using linear regression.
Results: Receipt of at least one dose of HPV vaccine was low in both females (35%) and males (10%). High BMI was not associated with initiation of the HPV vaccine series, age at first HPV vaccination, or completion of the HPV vaccine three-dose course.
Conclusions: We found no evidence that high BMI is associated with reduced initiation or completion of the HPV vaccination series, or age at initiation of the three-dose course among a general population sample of US adolescents. Our results suggest that efforts to increase HPV vaccine uptake need not consider targeting by weight status at this time.

1. Introduction

Human papillomaviruses (HPVs) are a group of highly transmissible viruses that can be transmitted sexually. Infection with HPV is common; the World Health Organization (WHO) qualitatively estimates that most adults will experience at least one infection during their lives, and that infection is usually cleared without serious health consequences [1]. Prevalence estimates of HPV infection in women range from approximately 33% in US 15–19 year olds to 54% in 20–24 year olds [2], and it is assumed that prevalence estimates are the same for US men [3]. Persistent infection with HPV can cause cancer of the vagina, vulva, penis, and anus, as well as certain types of head and neck cancers, and anogenital warts [1]. More than 150 different types of HPV have been identified, of which some 40 infect the genital area [4,5]. It is estimated that HPV types 16 and 18 ("high-risk" types) are responsible for the majority of cervical cancers worldwide [1,6]; an additional eleven types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66) are recognized as being "high-risk" cancer-causing types by WHO [7]. Types 6 and 11 ("low-risk" types) are not thought to generally cause cancer, but cause greater than 90% of genital warts and can present significant health risks to immunodeficient individuals [1,8].

Since 2006, a quadrivalent HPV vaccine (against HPV types 16, 18, 6 and 11) has been approved in the US for the prevention of HPV in females aged 9–26 years [9]; this same quadrivalent vaccine was approved for use in US males aged 9–26 years in late 2009 [10]. A bivalent HPV vaccine against types 16 and 18 was approved for use in US females aged 10–25 years in 2009 [11], and a 9-valent vaccine against types 6, 11, 16, 18, 31, 33, 45, 52, and 58 was approved for use in US females aged 9–26 in 2014 [12] and males aged 16–26 in 2015 [13]. The US Advisory Committee on Immunization Practices (ACIP) first recommended routine vaccination with HPV vaccine to females aged 11–12 in 2006 [14]; this recommendation was extended to males aged 11–12 in 2011 [15]. At present, ACIP

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recommends quadrivalent, bivalent, or 9-valent HPV vaccine to females aged 11–12 (but permissible for girls as young as 9), and catch-up vaccination for females aged 13–26 [14,16]. ACIP also recommends quadrivalent or 9-valent HPV vaccine to males aged 11–12 (but permissible for boys as young as 9), and catch-up vaccination for males 13–21, while noting that quadrivalent and 9-valent HPV vaccine "may be given" to males 21–26 as well [15,16].

These vaccines have been found to be effective and cost-effective in preventing disease and precursors to disease [15,17]; recipients are recommended to receive three doses over the course of six months [18,19]. In order to maximize the direct and indirect benefits of HPV vaccination, high vaccine coverage must be achieved and maintained, especially among those at highest risk of HPV infection and HPV-associated cancers. The US Department of Health and Human Services' Healthy People 2020 goal for HPV vaccine uptake is 80% for both female and male adolescents 13–15 years old [20]. However, nationwide coverage of at least one dose of HPV vaccine was estimated to be 60% among females aged 13–17 years and 42% for males aged 13–17 years in 2014 [21]. Other studies have noted geographic variation in vaccine uptake [22] and differences in uptake by gender [23,24], parental characteristics [25], and health insurance type [26].

To effectively increase HPV vaccine coverage, it is necessary to identify those least likely to be vaccinated and, thus, most likely to benefit from a targeted vaccination program. Evidence indicates that vaccine coverage is low in women of lower socioeconomic status (SES) [27], older age [27,28], lower education [22], and women of racial/ethnic minority status [29]. Recent research suggests that women with higher BMI in a low-income population have lower uptake of HPV vaccine [30]. This finding raises questions about whether individuals with high BMI in the general US population should be the focus of targeted vaccination campaigns. In addition, targeted vaccination by BMI may be especially beneficial because some research quantifying the risk of adolescent and adult HPV infection suggests that STI risk may be higher in women with higher BMI [31], though other studies have failed to find such a relationship [32–34].

Additional research is needed to investigate whether BMI is associated with HPV vaccine series initiation and/or completion among the general population of US adolescents. Plausible mechanisms for such a relationship include well-documented weight-related stigma in the healthcare setting, which may extend to access to vaccines for high-BMI individuals [35,36]. If BMI is associated with vaccine series initiation or completion among US adolescents, this may suggest the need for a targeted intervention to improve vaccination coverage.

We assessed whether US adolescents with high BMI may be at risk for low vaccine uptake. We used publicly available data from the US National Health and Nutrition Examination Survey (NHANES), a large-scale, nationally representative survey with in-person interviews and physical exams, to investigate whether overweight or obese US adolescents are 1) less likely to initiate HPV vaccination, 2) less likely to complete the HPV vaccine three-dose series, and/or 3) more likely to initiate the HPV vaccination at a later age.

2. Methods

2.1. Setting and participants

NHANES is a national survey conducted by the US Centers for Disease Control and Prevention (CDC) to study the health and nutritional status of children and adults [37–39]. Individuals over 6 months of age are selected using a multistage probability sampling design to ensure a population-representative sample. Participants are interviewed about their health and habits, and undergo a physical examination where height and weight are measured [38,39]. Details of the sampling methods, population weights, and other characteristics of the data have been described previously [38,39].

2.2. Measures

We restricted this analysis to all adolescent NHANES participants aged 9–18 years who were asked about HPV vaccination status (this included both females and males in 2011–2012 and 2013–2014, and females only in 2009–2010). Data for those aged 11–18 was self-reported, while data for those under 11 years old was provided by parents or guardians [40].

2.2.1. Body mass index

In the 2011–2012 and 2013–2014 NHANES, BMI was categorized according to age- and sex-specific percentiles in the 2000 CDC growth charts [41]; we used the SAS code provided by the CDC to categorize BMI in the same way for 2009–2010 NHANES data [42]. BMI was categorized as underweight (under the 5th percentile), normal (the 5th to less than the 85th percentile), overweight (the 85th to less than the 95th percentile), and obese (those at or above the 95th percentile).

2.2.2. Covariates

We identified potential confounders likely to be associated with BMI and HPV vaccine receipt a priori. These included: ratio of household income to federal poverty level (measured as a continuous variable), age at interview (dichotomized at 9–12 and 13–18 years old), race/ethnicity (dichotomized into non-Hispanic White vs. Mexican-American, non-Hispanic Black, other Hispanic, and other), and NHANES data cycle (when data from more than one cycle were available for analysis).

2.2.3. HPV vaccine uptake

NHANES began asking female participants about HPV vaccine uptake in 2009; in 2011, NHANES also began asking male participants about HPV vaccine uptake. We assessed the relationship between BMI and initiation of the HPV vaccination series (as a binary outcome), completion of the HPV vaccination series (as a binary outcome), and age at first vaccine receipt (as a continuous outcome).

2.3. Statistical analysis

We used modified Poisson regression with robust variance estimation to assess the relationship between weight status and both initiation and completion of the HPV vaccine three-dose course. Modified Poisson regression results closely approximate risk ratios obtained by standard methods, and thus provide an appropriate alternative modeling approach for common dichotomous outcomes when log-binomial models fail to converge [43]. We used linear regression to assess the relationship between weight status and age at first vaccine receipt. For all models, potential confounders that were identified at the outset (described above) were included. Population proportions were calculated by levels of BMI using the Stata *svyset* module. Post-estimation probabilities of HPV uptake were estimated from adjusted Poisson models using the Stata *margins* module; probabilities were estimated keeping all other variables [ratio of household income to federal poverty level (measured as a continuous variable), age at interview (dichotomized at 9–12 and 13–18 years old), race/ethnicity (dichotomized into non-Hispanic White vs. Mexican-American, non-Hispanic Black, other Hispanic, and other), and NHANES data cycle (when data from more than one cycle were available for

Table 1
Characteristics of study participants according to HPV vaccine uptake status.

Characteristic	Overall	No HPV vaccine doses received	At least one HPV vaccine dose received	*P* value
Females				
Age (yrs): mean ± SD	13.2 ± 2.9	12.5 ± 2.9	14.6 ± 2.3	<0.001
Age group (yrs): *N* (%)				<0.001
9–12	1114 (45.1)	944 (57.3)	170 (20.7)	<0.001
13–18	1355 (54.9)	704 (42.7)	651 (79.3)	
Ratio of household income to federal poverty level: mean ± SD	1.9 ± 1.5	1.9 ± 1.5	1.8 ± 1.5	0.06
Has health insurance: *N* (%)	2188 (88.8)	1438 (87.4)	750 (91.6)	0.002
BMI category: *N* (%)				0.04
Underweight	70 (2.8)	58 (3.5)	12 (1.5)	
Normal weight	1465 (59.3)	972 (59.0)	493 (60.1)	
Overweight	422 (17.1)	279 (16.9)	143 (17.4)	
Obese	512 (20.7)	339 (20.6)	173 (21.1)	
Ethnicity: *N* (%)				0.19
Non-Hispanic White	663 (26.9)	456 (27.7)	207 (25.2)	
All others[a]	1806 (73.2)	1192 (72.3)	614 (74.8)	
US citizen: *N* (%)	2283 (92.6)	1520 (92.4)	763 (92.9)	0.63
Year of data release				0.01
2009–2010	825 (33.4)	584 (35.4)	241 (29.4)	
2011–2012	775 (31.4)	504 (30.6)	271 (33.0)	
2013–2014	869 (35.2)	560 (34.0)	309 (37.6)	
Males				
Age (yrs): mean ± SD	13.2 ± 2.9	13.0 ± 2.9	14.1 ± 2.4	<0.001
Age group (yrs): *N* (%)				<0.001
9–12	729 (44.5)	648 (47.5)	81 (29.4)	<0.001
13–18	911 (55.6)	716 (52.5)	195 (70.7)	
Ratio of household income to federal poverty level: mean ± SD	1.9 ± 1.5	1.9 ± 1.5	1.8 ± 1.5	0.49
Has health insurance: *N* (%)	1469 (89.7)	1212 (89.1)	257 (93.1)	0.04
BMI category: *N* (%)				0.20
Underweight	55 (3.4)	51 (3.7)	4 (1.5)	
Normal weight	955 (58.2)	788 (57.8)	167 (60.5)	
Overweight	287 (17.5)	235 (17.2)	52 (18.8)	
Obese	343 (20.9)	290 (21.3)	53 (19.2)	
Ethnicity: *N* (%)				0.05
Non-Hispanic White	4410 (25.0)	354 (26.0)	56 (20.3)	
All others[a]	1230 (75.0)	1010 (74.1)	220 (79.7)	
US citizen: *N* (%)	1519 (92.7)	1260 (92.4)	259 (93.8)	0.42
Year of data release				<0.001
2011–2012	777 (47.4)	699 (51.3)	78 (28.3)	
2013–2014	863 (52.6)	665 (48.8)	198 (71.7)	

[a] "All others" includes Mexican-American, non-Hispanic Black, other Hispanic, and other.

analysis)] in the adjusted models at their respective means. Statistical analysis was completed using Stata 14.1 IC (College Station, TX); age- and sex-specific BMI percentiles for 2009–2010 NHANES were calculated in SAS 9.4 (Cary, NC) using CDC-provided SAS code [42].

3. Results

Of the 4431 NHANES participants aged 9–18 years old in 2009–2010, 2011–2012 or 2013–2014 who were asked questions related to HPV vaccine receipt, 34 had missing values for BMI category and 288 had missing values for HPV vaccine receipt, and were thus excluded from the analysis. Most of the remaining 4109 participants were of normal weight (58.9% (*N* = 2420)), while 20.8% (*N* = 855) were obese, 17.3% (*N* = 709) were overweight, and 3.0% (*N* = 125) were underweight; the mean ± SD for age was 13.2 ± 2.9 years. A total of 2469 females (60.1% of sample) and 1640 (39.9% of sample) males were included in the final analysis (more females were included than males because females answered HPV-related questions in all data release periods, whereas males only answered HPV-related questions in 2011–2012 and 2013–2014) (Table 1). Of females, 1648 (66.7%) reported not having received any HPV vaccine, while 821 (33.3%) reported receiving at least one dose. Of those who received at least one dose, 433 (52.7%) reported having received all three doses. Of the males, 1364 (83.2%) reported not having received any HPV vaccine; 276 (16.8%) reported having received at least one dose; and 118 (42.8%) of those receiving at least one dose reported having received all three doses.

In adjusted Poisson regression analyses, overweight and obesity were not significantly associated with initiation of the HPV vaccine series for females or for males, though there was an association between female underweight and reduced likelihood of having received any HPV vaccine (Table 2). Similarly, overweight and obese BMI were not significantly associated with completion of the three-dose series, though there was an association between male underweight and increased likelihood of having completed the three-dose series (Table 3). In linear regression analyses for females and males, overweight and obesity were not significantly associated with the age at first receipt of HPV vaccine after controlling for potential confounders, although there was an association between female underweight and younger age at first receipt of HPV vaccine (Table 4).

After applying population weights to account for the complex survey design, an overall estimated 35% of females and 10% of males had initiated the HPV vaccine series; a slightly smaller proportion of underweight adolescents (males and females) had initiated the vaccine series compared to their normal-weight peers. These proportions were similar when estimating predicted probabilities from Poisson regression models (Table 5).

Table 2
Relative risk of initiating the HPV vaccination series among US adolescents with high and low BMI (compared to US adolescents with normal BMI).[a]

	Bivariate model		Adjusted model[b]	
	uRR	95% CI	aRR	95% CI
Females[c]				
Underweight	0.40	0.20–0.65	0.45	0.26–0.80
Normal weight	Ref	–	Ref	–
Overweight	0.90	0.71–1.12	0.93	0.75–1.15
Obese	0.93	0.76–1.12	0.94	0.76–1.15
Males[d]				
Underweight	0.36	0.12–1.13	0.39	0.13–1.18
Normal weight	Ref	–	Ref	–
Overweight	1.19	0.80–1.76	1.08	0.73–1.61
Obese	0.95	0.66–1.39	0.98	0.69–1.40

[a] uRR, unadjusted risk ratio. aRR, adjusted risk ratio.
[b] Adjusted model controls for ratio of household income to federal poverty level, age group, race/ethnicity and NHANES period.
[c] Model results for females are from 2009–2010, 2011–2012 and 2013–2014 NHANES data releases.
[d] Model results for males are from 2011–2012 and 2013–2014 NHANES data releases.

Table 3
Relative risk of completing the HPV vaccination series among US female and male adolescents with high and low BMI (compared to US adolescents with normal BMI).[a]

	Bivariate model		Adjusted model[b]	
	uRR	95% CI	aRR	95% CI
Female BMI status[c]				
Underweight	0.53	0.23–1.23	0.52	0.20–1.34
Normal weight	Ref	–	Ref	–
Overweight	0.80	0.65–0.98	0.85	0.68–1.05
Obese	0.89	0.76–1.04	0.93	0.77–1.12
Male BMI status[d]				
Underweight	2.07	1.49–2.87	2.18	1.49–3.21
Normal weight	Ref	–	Ref	–
Overweight	1.37	0.88–2.13	1.33	0.80–2.21
Obese	0.61	0.37–1.01	0.60	0.34–1.06

[a] uRR, unadjusted risk ratio. aRR, adjusted risk ratio.
[b] Adjusted model controls for ratio of household income to federal poverty level, age group, race/ethnicity and (for females only) NHANES period.
[c] Model results for females are from 2009–2010, 2011–2012 and 2013–2014 NHANES data releases.
[d] Model results for males are from 2013–2014 NHANES data release only.

Table 4
Relationship between high and low BMI and age at first receipt of HPV vaccine (measured continuously in years) in US female and male adolescents.[a,b]

	Bivariate model		Adjusted model[c]	
	β_{unadj}	95% CI	β_{adj}	95% CI
Females[d]				
Underweight	−0.52	−1.41–0.38	−1.07	−1.76–−0.39
Normal weight	Ref	–	Ref	–
Overweight	0.24	−0.24–0.73	0.30	−0.17–0.78
Obese	−0.11	−0.72–0.50	0.06	−0.55–0.67
Males[e]				
Underweight	−0.36	−2.04–1.31	−0.19	−1.86–1.49
Normal weight	Ref	–	Ref	–
Overweight	0.61	−1.30–2.52	0.18	−1.21–1.58
Obese	−0.25	−1.71–1.20	−0.02	−1.03–1.00

[a] β_{unadj}, unadjusted beta estimate. β_{adj}, adjusted beta estimate.
[b] A one-unit increase in β indicates a one-year increase in the age at first HPV vaccine receipt; negative values for β indicate younger age at first HPV vaccine receipt.
[c] Adjusted model controls for age at interview, ratio of household income to federal poverty level, race/ethnicity, and (for females only) NHANES period.
[d] Model results for females are from 2009–2010, 2011–2012 and 2013–2014 NHANES data releases.
[e] Model results for males are from 2013–2014 NHANES data release only.

4. Discussion

We found no evidence that higher BMI is associated with lower probability of HPV vaccine uptake, or with older age at first vaccine receipt, in male or female adolescents. We also found no evidence to suggest an association between higher BMI and lower probability of completion of the HPV vaccine three-dose course in female or male adolescents. These findings indicate that overweight and obese adolescents are not at increased risk for low HPV vaccine uptake, or delayed uptake, compared to their normal-weight peers. We find no evidence that adolescents with higher BMI should be broadly targeted for increasing HPV vaccine uptake, as previously suggested [30].

However, our results confirm previous findings that HPV vaccine uptake is still low among both male and female adolescents, compared to the Healthy People 2020 goal of 80% coverage [20]. Low overall vaccine uptake and a high number of missed vaccination opportunities, especially among males and younger adolescents of both sexes, have been reported previously [22,26,44]. The lower probability of vaccine uptake in males compared to females may be related to the more recent recommendation for vaccination of males.

Table 5
Population proportion of those initiating HPV vaccination and predicted probability of initiating HPV vaccination, by BMI category, in US adolescents.

	Population proportion initiating HPV vaccination	Predicted probability of HPV vaccine initiation[a]	
		Probability	95% CI
Females			
Underweight	0.13	0.14	0.05–0.22
Average	0.37	0.30	0.26–0.34
Overweight	0.33	0.28	0.22–0.34
Obese	0.34	0.28	0.22–0.34
Males			
Underweight	0.01	0.01	0.0[b]–0.04
Average	0.10	0.10	0.06–0.14
Overweight	0.11	0.09	0.02–0.15
Obese	0.08	0.08	0.03–0.13

[a] Predicted probabilities are calculated using adjusted regression models described above, controlling for ratio of household income to federal poverty level, age, race/ethnicity, and NHANES data release cycle. All regression covariates are kept constant at their respective means.
[b] The lower bound for this probability estimate was calculated at −0.02, but was truncated at zero to provide clarity regarding the possible range of probabilities.

Our analysis was conducted using NHANES data, where physical examination is done by trained research staff, eliminating possible self-report biases of measures such as height and weight [38,39]. Data collected from NHANES is reviewed by statisticians for accuracy, including missed skip patterns and extreme values, which ensures high data quality [37]. NHANES is a cross-sectional, observational study that relies on individual self-report for health information and vaccination status, which could be subject to recall bias. However, rates of HPV uptake based on NHANES data are similar to national estimates drawn from the National Immunization Survey (NIS) over the same time period among adolescents of similar age [45]. The NIS asks similar questions about vaccine uptake, but also contacts physicians to confirm self-reported vaccination status based on medical records. A study of the accuracy of self-reported receipt of any HPV vaccine compared with medical records used in NIS found high sensitivity and specificity among adults [46], though it is not clear how these results would apply to adolescents or for recall about the age at vaccination and completion of a vaccine series. Another study on the validity of parental recall for adolescent vaccines indicated low bias for HPV4 vaccine recall with sensitivity of 95% and specificity of 97% for receipt of at least one HPV vaccine dose; potential bias was similarly low for reports of at least one dose compared to completion of the 3-dose series [47].

CDC notes that two adjacent NHANES data cycles may be combined to solve potential statistical instability problems resulting from sparse data [39]. Because NHANES began assessing HPV vaccine uptake in males in 2011, we had access to data from two data cycles of NHANES; however, ACIP recommendations for males to receive HPV vaccine were issued late in 2011 [15], resulting in a comparatively shorter period of time for males to be vaccinated. This resulted in low statistical power to assess the relationship between BMI and HPV vaccination initiation in males. In addition, we were not able to account for the possible confounding effect of healthcare utilization behavior across different strata of BMI because the way in which healthcare utilization was captured changed between the 2011–2012 and 2013–2014 data cycles. When we conducted the analyses using the first and second cycle of data only with and without adjustment for healthcare utilization, we observed similar model results for females in all models and males for first receipt of HPV. An additional analysis utilizing only the 2013–2014 data cycle indicated no additional benefit of including a healthcare seeking variable in models describing completion of the 3-dose course for males, or age at first vaccination for males. Finally, though current CDC growth chart cutoffs are standard for categorizing BMI, they are based on weight and height information from 1963 to 1994 and may not reflect clinically relevant weight categories.

Interestingly, we found some evidence that underweight males, on average, initiated the HPV vaccine course at a younger age than their male normal-weight peers and were more likely to complete the series. Further research in a larger sample of males is needed to confirm this finding and determine other possible factors that may explain this association. We also found an association between female underweight and a reduced likelihood of initiating the HPV vaccine series, as well as an association between female underweight and an earlier age of initiating the HPV vaccine series. These findings may be due to sparse data (less than 3% of females were underweight), but may warrant further investigation in a larger sample of female adolescents.

5. Conclusions

Our analyses indicate that high BMI is not associated with initiation or timing of the three-dose HPV vaccine course in US males or females aged 9–18 years. High BMI also is not associated with completion of the HPV vaccine three-dose course in US females aged 9–18 years. Our findings highlight the overall low uptake of HPV vaccine compared to national targets. This study reinforces the need for efforts to increase HPV vaccine uptake in adolescents across all BMI categories.

Conflicts of interest

The authors report no conflicts of interest.

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Contributions

NEB originally conceived of the research question. MES had primary responsibility of statistical analysis and manuscript writing. NEB and SMM provided writing and analytic support. All authors contributed significantly to the final manuscript.

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