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Socioeconomic predictors of human papillomavirus vaccination in Danish men – A nationwide study



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ABSTRACT

Background: The quadrivalent human papillomavirus vaccine was licensed in Denmark in 2006. Unlike women, men are not offered human papillomavirus vaccination free of charge but can have it at their own expense. We investigated human papillomavirus vaccine uptake by men in Denmark and the socioeconomic factors that may predict human papillomavirus vaccination.

Methods: Using the Civil Registration System, we identified all boys and men aged 9–26 years in 2006–2013 and their mothers. By linkage to Statistics Denmark and the National Prescription Registry, we obtained information on socioeconomic variables and human papillomavirus vaccination during the study period. Using Cox regression, we examined the associations between socioeconomic variables and human papillomavirus vaccination.

Results: Between 2006 and 2013, 6253 (0.8%) males aged 9–26 years were vaccinated against human papillomavirus. The strongest predictor identified was ethnicity. Males who were immigrants (hazard ratio, 0.12; 95% confidence interval, 0.08–0.180) or sons of immigrant parents (hazard ratio, 0.13; 95% confidence interval, 0.10–0.17) were less likely to be vaccinated than Danish males. Additionally, sons of mothers who were unemployed, unmarried, had a low income, and basic education initiated human papillomavirus vaccination less frequently. Finally, sons of mothers who were physicians or nurses were more likely to be vaccinated than sons of other highly educated mothers.

Conclusion: We found low uptake, with social disparities in human papillomavirus vaccination of boys and young men in Denmark.

1. Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections. Persistent infection with high-risk HPV types is associated with cervical cancer, which is the fourth most common cancer in women worldwide [1]. HPV is also associated with a number of other anogenital and oropharyngeal cancers, many of which also affect men [2]. Additionally, low-risk HPV types are associated with genital warts, which are common in both women and men [3].

Currently, three vaccines against HPV are available, and more than 57 countries have started national HPV immunization programmes since 2007. Most of these programmes are directed to women, as cervical cancer is the most common HPV-related cancer [3]; however, there is an ongoing discussion about whether boys and men should also be included in HPV immunization programmes, which would not only

protect men but would probably increase the protection of women through a herd effect.

The quadrivalent HPV vaccine has been found to be effective and generally well tolerated in both women and men [3–5]. For boys, the vaccine has been approved by the European Medicines Agency and the United States Food and Drug Administration for the prevention of anal cancers, anal precancerous lesions, and genital warts [4,5]. Since 2013, Australia has vaccinated 12–13-year-old boys free of charge [6]. Likewise, both Canada and the USA recommend routine HPV vaccination of adolescent boys [7,8]. In Europe, Austria is the only country that includes males in the national HPV immunization programme [9].

In Denmark, HPV vaccine was included for girls in the childhood vaccination programme in January 2009, and the first catch-up programme for girls up to 15 years of age started in October 2008; the second free catch-up vaccination programme, starting in August

Abbreviations: HPV, human papillomavirus; ATC, anatomical therapeutic chemical; HR, hazard ratio; CI, confidence interval

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2012, covers women up to 27 years of age. The programme has reached high coverage: 75–91% of eligible girls receive at least one dose, and the majority of those who initiate vaccination complete the programme [6,7]. Boys and men are not included in the vaccination programme, but, since licensure of the quadrivalent HPV vaccine in 2006, they have been able to purchase the vaccine at their own expense.

To our knowledge, there are no studies on HPV vaccine uptake among boys in Europe. Several studies on the acceptability of HPV vaccination by young men and parents of boys show good acceptability and identify knowledge about HPV and the HPV vaccine as the most influential factor in the decision to be vaccinated [8–12]. A Danish study also showed a high level of acceptability of HPV vaccination among parents of 12–15-year-old boys. Although 45% were willing to cover the cost of vaccination, this does not necessarily predict high uptake [13,14]. HPV vaccination uptake among adolescent boys has been studied in the USA, where several studies showed that racial and socioeconomic factors are associated with uptake [15–20]. Most of the studies were based on surveys and were conducted after routine HPV vaccination of boys and men was recommended in the USA.

The aim of this population-based register study was to determine nationwide HPV vaccine uptake among boys and men in Denmark and the socioeconomic and demographic factors that might predict initiation of vaccination. As knowledge about HPV has been shown to be an important predictor of acceptability [13] of vaccination, we also studied whether sons of health care professionals are more likely to receive HPV vaccination.

2. Methods

In Denmark, each citizen is assigned a 10-digit personal identification number, which can be used as key identifier when linking individual information between national registers. From the Civil Registration System, we identified all boys and men aged 9–26 years living in Denmark in 2006–2014 and included them in an open cohort. The participants entered the cohort on 1 October 2006, or at the time of their 9th birthday, whichever came last. We continued follow-up until 30 June 2014, their 26th birthday, or date of emigration or death, whichever occurred first. We also identified the parents of the study population and obtained data on their socioeconomic variables from population-based registers at Statistics Denmark. The study protocol was approved by the Danish Data Protection Agency.

To identify vaccinated boys and men, we linked the cohort to the Danish National Prescription Register, which contains data on all prescriptions redeemed in Danish community pharmacies. HPV vaccines are identified by anatomical therapeutic chemical (ATC) codes. We obtained information on all males in the cohort who redeemed at least one prescription for either the bivalent (ATC-code J07BM02) or the quadrivalent HPV vaccine (ATC-code J07B01).

We used ethnicity, income, education, employment status, and marital status as indicators of socioeconomic status of the mothers. We also identified mothers who were physicians or nurses. All measures were of the mothers of the boys and men in the study population, except for ethnicity, which was determined for the males themselves. If data were not available on the mother, information on the father was used instead.

Ethnicity was divided into three categories: Danish (both mother and son born in Denmark), descendant (mother born outside Denmark, son born in Denmark), and immigrant (son born outside Denmark). Education was divided into basic (primary school), vocational (high school, secondary school or vocational education), and higher (bachelor or higher university degree). In an additional analysis of education, we categorized nurses and physicians in separate groups. Disposable income was calculated as income after deduction of taxes, divided into tertiles, and categorized as low, middle, or upper. Employment status was categorized as employed, unemployed, and uncategorized, which included housewives and students. Marital status

was categorized as married, widowed, divorced, or unmarried.

2.1. Statistical analysis

We used Kaplan-Meier plots to illustrate the cumulative probability of vaccination according to attained age. We constructed plots for ethnicity, mother's education, income, employment status, and marital status. We additionally plotted education to include the sons of physicians and nurses as separate categories. We used a Cox proportional hazards model to compare vaccination initiation stratified by birth cohort, using attained age as the underlying time scale. We calculated both crude hazard ratios (HRs) and mutually adjusted HRs for participants for whom complete information on all the variables was available and mutually adjusted HRs with all those for whom data were missing, included as a separate category "unknown". We made the same calculations for boys who received three vaccine doses. As almost all who initiated vaccination also completed the regime, and as we found the same socio-economic pattern in initiation and completion of vaccination, we only show data for initiation of HPV vaccination.

The proportional hazards assumption was tested with scaled Schoenfeld residuals, which showed a significant trend after the age of 18 years for ethnicity and education of the mother. Thus, we fitted separate models for 9–18-year-olds and 19–26-year-olds for those variables. The statistical analyses were performed with the statistical software R, version 3.1.2. [21] The level of significance was set to 5%, and two-sided tests were used in all analyses.

3. Results

A total of 809,656 boys and men were included in the study, of whom 6253 (0.8%) initiated HPV vaccination and 4283 completed the regime with three doses during 2006–2014. Most were vaccinated towards the end of the period, so the difference between the number who initiated and completed vaccination reflects that many did not have time to complete vaccination before 2014. Almost half of those who were vaccinated (49%) were 12–15 years old, while 24% were 16–18 years, 3% were younger than 12 years, 14% were 19–22 years and 10% were 23–26 years old at initiation of HPV vaccination. Table 1 shows the characteristics of the vaccinees and socioeconomic characterization of the mothers. The percentage of vaccinated boys and men was low in all birth cohorts, ranging from 0.03% in the 1979–1984 birth cohort to 1.9% in the 1994–1999 birth cohort.

Fig. 1 shows the probability of initiation of vaccination with age as the underlying timescale stratified by ethnicity and indicators of the mother's socioeconomic status (education, disposable income, employment status, and marital status). The figure shows a low probability for initiation of vaccination among all boys and men, regardless of socioeconomic position. There were, however, differences in the levels of socioeconomic predictors. For instance, vaccination was more likely among ethnic Danes than immigrants or descendants and among sons of mothers with a high income, mothers who were employed, and mothers who were married. In relation to the mother's education, we found that sons of women with a high level of education were more likely to be vaccinated than those of women with vocational training or basic education. When nurses and physicians were analysed as separate categories (Fig. 2), the sons of mothers who were nurses or (especially) physicians had a higher probability of being vaccinated than the sons of other women with higher education.

We analysed the importance of the socio-economic indicators after adjustment for age and after mutual adjustment. Table 2 shows the relative probability of being vaccinated in relation to socioeconomic status, expressed as unadjusted and mutually adjusted hazard ratios. We found a strong correlation between vaccine initiation and ethnicity. Immigrants (HR: 0.12 95% CI: 0.08–0.18) and descendants of immigrants (HR: 0.13 95% CI: 0.10–0.17) were less likely to initiate vaccination than ethnic Danes. Moreover, we found significantly less

Table 1
Characteristics of human papillomavirus-vaccinated boys and men aged 9–26 years in Denmark, 2006–2013.

Variable	Human Papillomavirus vaccination		
	n	Vaccinated %	
Birth cohort			
1979–1984	147,252	44	(0.03)
1984–1989	152,819	668	(0.4)
1989–1994	173,592	1427	(0.8)
1994–1999	172,793	3263	(1.9)
1999–2001	66,362	727	(1.1)
2001–2004	96,838	124	(0.1)
Age at vaccination (years)			
< 12		179	
12–15		3073	
16–18		1510	
19–22		877	
23–26		614	
Boy's or man's ethnicity			
Danish	714,133	6161	(0.9)
Descendant	43,539	57	(0.1)
Immigrant	34,683	24	(0.8)
Unknown	11,048	11	(0.1)
Mother's education			
Higher	253,979	3601	(1.4)
Vocational	375,028	2216	(0.6)
Basic	142,495	378	(0.3)
Unknown	38,154	58	(0.2)
Mother's income			
High	272,582	3794	(1.4)
Middle	276,808	1601	(0.6)
Low	239,519	829	(0.4)
Unknown	20,747	29	(0.1)
Mother's employment status			
Employed	627,302	5700	(0.9)
Unemployed	139,215	372	(0.3)
Uncategorized	22,392	152	(0.7)
Unknown	20,747	29	(0.1)
Mother's marital status			
Married	551,267	4973	(0.9)
Widow	9061	34	(0.4)
Divorced	96,241	511	(0.5)
Unmarried	118,492	651	(0.6)
Unknown	34,595	84	(0.2)

initiation among sons of mothers with vocational (HR: 0.43 95% CI: 0.40–0.45) or basic (HR: 0.17 95% CI: 0.16–0.19) education than among those of mothers with higher education. Likewise, we found a significant difference in vaccine initiation by the income and employment status of the mother. High income was associated with a greater likelihood of initiation than middle income (HR: 0.43 95% CI: 0.41–0.46) or low (HR: 0.30 95% CI: 0.28–0.32), and sons of unemployed mothers (HR: 0.31 95% CI: 0.28–0.35) were less likely to be vaccinated than sons of employed mothers. Finally, the sons of married mothers were more likely to be vaccinated than those of unmarried mothers (HR: 0.58 95% CI: 0.53–0.63), widowed mothers (HR: 0.68 95% CI: 0.48–0.95), or divorced mothers (HR: 0.61 95% CI: 0.56–0.67).

In the mutually adjusted model, we found similar results for most of the variables. The only substantial difference was that uncategorized employment of the mother appeared to significantly increase the likelihood of vaccination of a son as compared with the sons of employed mothers (HR: 1.83 95% CI: 1.53–2.18). In a sensitivity analysis, we included participants for whom information was missing information ("unknown" in the mutually adjusted model); this did not significantly alter any of the calculated HRs (data not shown).

When we tested the assumption of proportionality, we found a change in the relative hazard of some variables around the age of 19 years. We therefore calculated separate HRs for 9–18-year-olds and 19–26-year-olds for all variables and tested whether there was a significant difference between the HRs by age group (data not shown). The effects of both ethnicity and mother's education were significantly smaller in 19–26-year-olds than in younger boys, although the general pattern was the same. The HR for being vaccinated was 0.06 (95% CI: 0.03–0.13) for immigrants aged 9–18 years when compared with ethnic Danes, while that of 19–26-year-old immigrants was 0.20 (95% CI: 0.13–0.33). A similar result was found for sons of immigrants (HR_{9–18}: 0.11; 95% CI: 0.08–0.15; HR_{19–26}: 0.25; 95% CI: 0.16–0.41). Likewise, sons of mothers with basic education had an HR of being vaccinated of 0.15 (95% CI: 0.13–0.17) in the younger age group and 0.27 (95% CI: 0.22–0.32) in the older age group when compared with sons of mothers with high education. Sons of mothers with vocational training were also less likely to be vaccinated than sons of mothers with high education (HR_{9–18}: 0.41; 95% CI: 0.39–0.44; HR_{19–26}: 0.47; 95% CI: 0.42–0.53).

4. Discussion

In this nationwide register-based cohort study, we found a low uptake of the HPV vaccine (0.8%) among Danish boys and men aged 9–26 years in 2006–2014. Moreover, we found substantial social inequality in vaccination, with less uptake and completion of a three dose vaccination regime among more socioeconomically disadvantaged boys (measured by employment status, income, education, and marital status of the mother). Likewise, less uptake and completion were found among immigrants and descendants of immigrants, even after adjustment for the other indicators of socioeconomic status. Sons of mothers who were physicians or nurses were more likely to be vaccinated than sons of mothers with other higher education.

In line with our results, a study in the USA showed low male uptake of HPV vaccination before routine vaccination of men was recommended [19]. In 2010, only 2% of 11–17-year-old boys had received at least one dose of the quadrivalent HPV vaccine [19].

In the present study, one of the most influential predictors of HPV vaccination was ethnicity, ethnic Danes being significantly more likely to be vaccinated than either immigrants or descendants. This finding is in line with previous studies on parents' acceptance of HPV vaccination for their sons [9,12]. Most studies on uptake in the USA, however, indicated that white citizens had a lower uptake than Hispanic and black citizens and immigrants [16–18,20]. In our study, the lower uptake by immigrants and descendants might be due to cultural or language barriers. Another contributing factor might be that immigrants in Denmark aged < 18 years have less contact with their general practitioner than non-immigrants [22]. They thus have less opportunity to receive information or a recommendation from their primary health care provider, which is an important predictor of HPV vaccination [23].

We found social disparities in respect of the mother's marital status, education, income, and employment, with a greater likelihood of vaccination if the mother was married, employed, had a high income, and had higher education. This finding is in line with that of a Danish study on HPV vaccine uptake by girls, which showed social disparities in uptake even when vaccination was free of charge in the HPV vaccination programme [24]. The 10–15% of girls in Denmark who are eligible for free HPV vaccination but are not vaccinated generally have lower socioeconomic status. In contrast, in the USA, studies on uptake by boys have found that higher education and income of the mother was either insignificant or associated with lower uptake [17,18,25]. The difference from our results may be due to the fact that US programs provide free vaccination for boys of lower socioeconomic status, while parents in Denmark have to cover the cost of vaccination for their sons. Moreover, our study was register-based, while the US

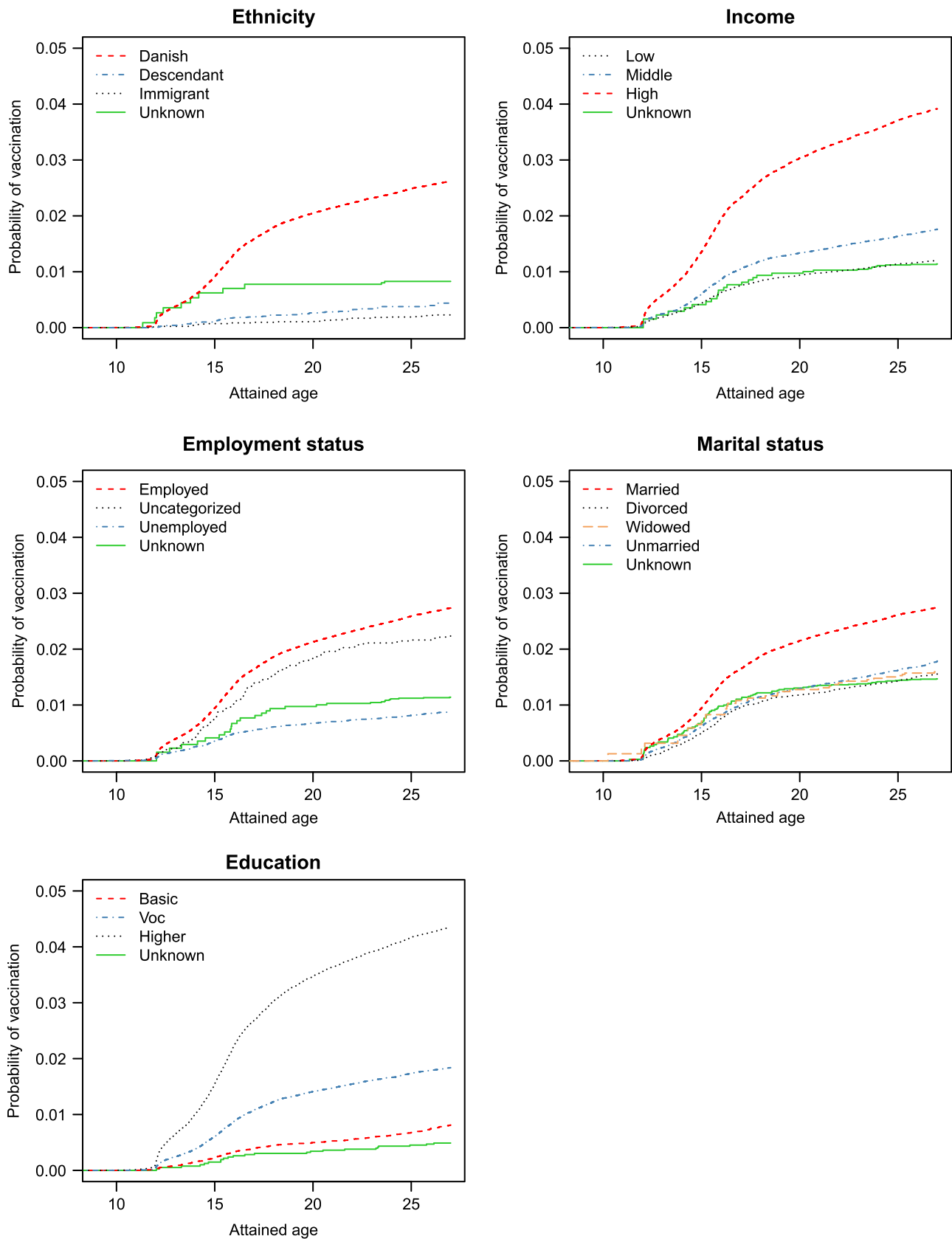


Fig. 1. Cumulative probability of boys and men receiving at least one dose of human papillomavirus vaccine by age 9–26 years, stratified by male ethnicity and the income, employment status, marital status, and education of the mother.

studies were based on surveys, which are more vulnerable to selection bias; i.e. people of high socioeconomic status respond more frequently. The probability of vaccination was much higher for sons of nurses

or physicians than for sons of other highly educated mothers. This is not surprising, as knowledge about HPV and HPV vaccination and a recommendation from a health care provider have been found to be the

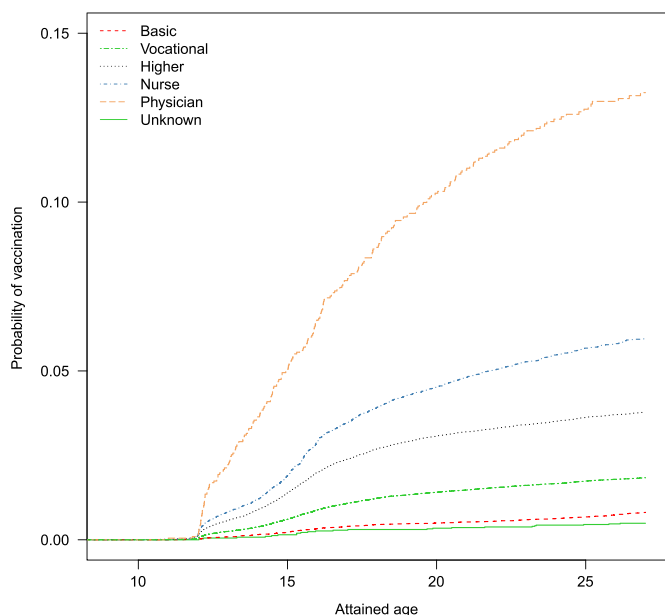


Fig. 2. Cumulative probability of boys and men receiving at least one dose of human papillomavirus vaccine by age 9–26 years, stratified by education of the mother.

Table 2

Hazard ratios (HRs) and 95% confidence intervals (CIs) for initiation of human papillomavirus vaccination based on indicators of socioeconomic status of Danish boys and men aged 9–26 years.

Variable	Unadjusted		Adjusted*	
	HR	95% CI	HR	95% CI
Boy's or man's ethnicity				
Danish	1	Reference	1	Reference
Descendant	0.13	0.10–1.17	0.22	0.17–0.29
Immigrant	0.12	0.08–0.18	0.20	0.13–0.30
Mother's education				
Higher	1	Reference	1	Reference
Vocational	0.43	0.40–0.45	0.52	0.50–0.55
Basic	0.17	0.16–0.19	0.28	0.25–0.31
Mother's income				
High	1	Reference	1	Reference
Middle	0.43	0.41–0.46	0.58	0.55–0.62
Low	0.29	0.28–0.32	0.53	0.48–0.58
Mother's employment status				
Employed	1	Reference	1	Reference
Unemployed	0.31	0.28–0.35	0.83	0.74–0.93
Uncategorized	0.81	0.69–0.95	1.83	1.53–2.18
Mother's marital status				
Married	1	Reference	1	Reference
Widow	0.68	0.48–0.95	0.72	0.51–1.01
Divorced	0.61	0.56–0.67	0.71	0.65–0.78
Unmarried	0.59	0.53–0.63	0.69	0.64–0.75

* Mutually adjusted.

most important predictors of vaccine uptake or acceptability [11,13,17,18,25,26]. Physicians and nurses are expected to be more knowledgeable about the benefits and drawbacks of vaccination than the general population. In Denmark, the HPV vaccine has been promoted mainly as a vaccine against cervical cancer, and some people may therefore not know that HPV-related diseases also affect men.

Furthermore, as routine HPV vaccination of boys is not recommended in Denmark, parents may consider that the risk of boys for HPV-related disease is not high. The social gradient in HPV vaccination frequency among boys and men found in our study may be due to the cost of the vaccine, so that it is affordable only for high-income families. It is also possible that parents with higher socioeconomic status are simply better informed about HPV and the HPV vaccine.

We chose to use predictors of the socioeconomic status only of the mother and not the father or the boy or man himself. In a similar study in Norway on predictors of HPV vaccination in girls and women, information on both the father and the mother was used; the socioeconomic status of the mother was found to be the stronger predictor [27]. In our study, the effects of ethnicity and the mother's education were significantly smaller after the age of 18 years, although still present. A likely explanation is that predictors of the socioeconomic status of boys become more important as they grow up.

An important strength of the study was the use of information from nationwide population-based registers and accurate linkage between them with the unique personal identification number, which limits the risk for recall bias, increases generalizability, and virtually eliminates loss to follow up. The potential limitations of the study include missing information on some socioeconomic determinants; however, this was minimal. If some boys were vaccinated without a prescription, perhaps because they were the sons of health care workers, this would have led to underestimation of the effect of socioeconomic factors on vaccine initiation, as the sons of health care workers generally have higher socioeconomic status. The determinants are highly correlated, and unadjusted estimates may be confounded by the other factors; however, even after mutual adjustment, the overall pattern did not change.

4.1. Conclusion

This study on HPV vaccine uptake among boys and men in Denmark, who are not covered by the national HPV immunization program, shows low uptake and significant social disparity.

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Conflicts of interest

Signe Bollerup and Christian Dehlendorff report no potential conflicts of interest. Birgitte Baldur-Felskov has received travel and speaker's fees from Sanofi Pasteur MSD. Susanne K. Kjaer has received advisory board and speaker's fees from Sanofi Pasteur MSD and from Merck, and unrestricted research grants through her institution from Merck.

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