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High-risk human papillomavirus seroprevalence in men and women of six different ethnicities in Amsterdam, the Netherlands: The HELIUS study

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ABSTRACT

Background: Ethnic variations in the (sero)prevalence of Human Papillomavirus (HPV) and HPV related diseases have been observed previously. We explored if high-risk HPV (hrHPV) seropositivity indeed differs among 6 ethnic groups in Amsterdam the Netherlands and assessed if hrHPV seroprevalence is higher among women than men within each ethnic group, both after adjustment for confounders.
Methods: From the multi-ethnic HEalthy Life In an Urban Setting (HELIUS) study in Amsterdam (the Netherlands) we randomly selected 4637 men and women aged 18–44 years with a Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Moroccan, or Turkish ethnicity. Blood samples were tested for HPV-16,–18,–31,–33,–45,–52, and –58 antibodies using a validated Luminex-based multiplex serology assay. We assessed the association of both ethnicity and gender with hrHPV seropositivity using logistic regression models with generalised estimating equations.
Results: The hrHPV seroprevalence in Dutch, South-Asian Surinamese, African Surinamese, Ghanaian, Moroccan, and Turkish participants was 18%, 12%, 23%, 19%, 17%, and 15% in men, and 30%, 22%, 34%, 31%, 14%, and 15% in women, respectively. HrHPV seroprevalence of non-Dutch men did not differ significantly from Dutch men. HrHPV seroprevalence was significantly higher among African Surinamese women, and significantly lower among Moroccan and Turkish women when compared to Dutch women. These differences were not significant anymore after adjustment for demographic, health, and sexual behavioural differences between ethnicities. HrHPV seroprevalence varied by age, age of sexual debut, and lifetime sexual partners among women but not among men. Seroprevalence of hrHPV was higher among women than among men, except in the Turkish group.
Conclusion: Among women hrHPV seroprevalence differed by ethnicity, yet among men no pronounced differences were observed across ethnicities.

1. Introduction

Prevalences of sexually transmitted infections (STI) such as Chlamydia trachomatis and Neisseria gonorrhoeae vary significantly between ethnicities in several industrialized countries [1–4], including the Netherlands [5–8]. Previous studies aiming to explain differences in STI prevalences between ethnic groups often showed that sexual behaviour explains a large fraction but not all of these differences [1,5,8].

Human papillomavirus (HPV) — an easily transmittable STI that, if persistent, can cause anogenital cancer and head and neck-cancer [9–11] — has shown prevalence disparities in HPV and HPV induced diseases among men and women across ethnicities/races within countries, and around the globe [12–15]. Sexual behavioural characteristics have shown to be key determinants for HPV (sero)positivity [16–20]. In the Netherlands, a country with an ethnically diverse

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population, limited data on HPV prevalences across ethnicities are available while it is known that incidence and mortality due to cervical cancer varies significantly by ethnicity [21–24].

In this study we investigated how the seroprevalence of high-risk HPV (hrHPV) varies by ethnicity separately for men and women, and, if disparities are observed, whether demographic, health, and sexual behavioural factors are able to explain these observed differences. We furthermore explored whether hrHPV seropositivity differs by age, age of sexual debut, and lifetime number of sexual partners across ethnic groups. Furthermore, as it is known that HPV infection of mucosal epithelium (i.e. the cervix and anal canal) induces a stronger humoral immune response than an HPV infection of keratinized epithelium (i.e. the shaft and the glans of the penis) [24–26], we aimed to confirm if hrHPV seroprevalence is indeed higher among women than among men, within each ethnic group. This study was executed within the HELIUS (HEalthy LIfe in an Urban Setting) study, a large multi-ethnic cohort study carried out in Amsterdam, the Netherlands (27).

2. Material and methods

2.1. Study population

Baseline data for this study were collected between 2011 and 2014. HELIUS randomly sampled participants from the municipality registry of Amsterdam, stratified by ethnicity. Included participants were 18–70 years old and from one of the five largest ethnic groups living in Amsterdam, i.e. people with a Dutch, Surinamese, Ghanaian, Moroccan, or Turkish origin [27]. Among individuals of Surinamese origin living in the Netherlands, the majority is of West-African or South-Asian (North Indian) origin, with a smaller proportion of Surinamese being of Javanese, Chinese, or other origin. The Surinamese group was subdivided into South-Asian Surinamese, African Surinamese, and an 'other' group, according to self-reported ethnic origin. The HELIUS study was approved by the AMC Ethical Review Board (protocol number:10/100; amendment10/100# 10.17.1729) and all participants provided written informed consent.

Ethnicity was based on the country of birth of the participant and the country of birth of both parents. A participant was considered of non-Dutch ethnic origin if he or she was (A) born outside the Netherlands and had at least one parent who was born outside the Netherlands (first generation) or (B) the participant was born in the Netherlands and both her/his parents were born outside the Netherlands (second generation) [27,28].

For the current study, we selected participants who were recruited between January 2011 and June 2014 (n=13,316). We excluded those who did not give permission to store biological samples, those of whom not enough blood was available to perform analyses, those with other/unknown ethnicity, those with a Surinamese origin other than South-Asian Surinamese or African Surinamese, and those aged > 44 years. This resulted in 5244 eligible participants (see Supplementary Fig. 1). We randomly selected up to 20 participants per life year, in the age range 18 through 44 years (=27 life years), from each gender and ethnic group, resulting in a theoretical maximum of 540 (=20×27) participants per ethnic group, per gender. This maximum was not always reached, as there were not always 20 participants available per gender and life year in each ethnic group. Participants vaccinated with a prophylactic HPV vaccine were excluded (Supplementary Fig. 1).

All participants completed a questionnaire and attended a physical examination during which biological samples were obtained. The questionnaire contained questions regarding socio-demographic characteristics (age, education, marital status, religion), health behavioural characteristics (HPV vaccination status, circumcision status, ever used oral contraceptives, and smoking behaviour), and sexual behavioural characteristics (ever had sex, age of sexual debut, number of lifetime sex partners [LSP], sexual activity in the preceding six months, condom use in preceding six months, gender of sexual partners, and tested for an STI in the preceding six months [including HIV]). Based on the gender of their sexual partners, participants were categorized into heterosexual (men who have had sex with women only / women who have sex with men only), men who have had sex with men (MSM) and women who have had sex with women (WSW).

2.2. HPV serology

Blood samples were centrifuged and stored at −20 °C within 2 h after collection and transported to −80 °C storage on the same day. Sera from selected participants were subsequently analysed with a multiplex serology assay according to standard protocols [29]. Reactivity of antibodies directed against the major capsid protein (L1) of mucosal hrHPV types 16, 18, 31, 33, 45, 52, and 58, and reactivity of E6 and E7 antibodies against the early oncoproteins of HPV 16 and HPV 18 were simultaneously analysed. L1, E6 and E7 antigens were expressed as Glutathione S-transferase (GST) fusion proteins in *Escherichia coli* as previously described [29]. Individual sets of spectrally distinct glutathione-casein-coupled fluorescence-labelled polystyrene beads (SeroMap, Luminex, Austin, TX) were loaded with different HPV type-specific antigens. For each bead set, the quantity of antibodies bound to the corresponding HPV type-specific antigen was determined as the median reporter fluorescence intensity (MFI) of at least 100 beads per bead set per serum. Final net MFI was obtained after subtraction of individual serum background (MFI derived from antibodies directed against fusion protein GST and tag without intervening viral antigen and bead set specific background). Net MFI were normalized such that the cutoffs of controls matched the cutoffs obtained in previous studies [30], resulting in cutoffs for seropositivity for individual HPV types varying between 400 and 700 MFI. Seroprevalence of any hrHPV was based on being seropositive for at least one of the hrHPV types tested.

2.3. Statistical analyses

We used Pearson's Chi-squared test and the Kruskal-Wallis test to compare categorical and continuous baseline characteristics between ethnic groups by gender.

We compared hrHPV seroprevalence across ethnic groups separately for men and women using Pearson's Chi-squared test. We estimated the probability of hrHPV seropositivity as a function of age in years, age of sexual debut, and LSP using restricted cubic spline standard logistic regression models with 4 knots (at 5%, 35%, 65%, and 95%). We tested for interactions between ethnicity and one of these three determinants (age in years, age of sexual debut, and LSP) with hrHPV seropositivity as outcome, using logistic regression models with generalised estimating equations (GEE) ($p \leq 0.100$ was considered a significant interaction). If interaction was significant at a $p < 0.100$, the probability of hrHPV seropositivity was presented separately for each ethnicity.

We used logistic regression models with GEE to investigate the association between ethnicity and hrHPV seropositivity. We adjusted the association between hrHPV seropositivity and ethnicity for age (model 1), age and sociodemographic determinants (education, marital status and religion) (model 2), age, sociodemographic and health related determinants (smoking, circumcision status [among men] and oral contraceptive use [among women]) (model 3), and age, sociodemographic, health related and sexual behavioural determinants (STI [including HIV] test behaviour in the past 6 months and LSP) (model 4). These variables were selected *a priori*.

We performed sensitivity analyses to explore whether excluding MSM and WSW would lead to different results, as it is known that MSM are more often hrHPV seropositive than heterosexual men [24]. We performed additional sensitivity analyses among participants 18–34 years of age, because detailed questions on sexual behaviour were optional for those who were ≥35 years, and were only completed by

Table 1
High-risk HPV seroprevalence among men aged 18–44 years, by ethnicity, the HELIUS study Amsterdam, the Netherlands, January 2011 - June 2014.

	Dutch		South-Asian Surinamese		African Surinamese		Ghanaian		Moroccan		Turkish			Total	
	(N=368)		(N=381)		(N=248)		(N=210)		(N=396)		(N=471)		p*	(N=2074)	
	n	%	n	%	n	%	n	%	n	%	n	%		n	%
High risk HPV[a]	68	18%	47	12%	56	23%	40	19%	66	17%	70	15%	**0.015**	347	17%
HPV 16 L1	17	5%	18	5%	13	5%	10	5%	15	4%	19	4%	0.953	92	4%
HPV 18 L1	12	3%	12	3%	16	6%	10	5%	10	3%	11	2%	0.056	71	3%
HPV 31 L1	31	8%	18	5%	24	10%	8	4%	17	4%	23	5%	**0.007**	121	6%
HPV 33 L1	7	2%	9	2%	9	4%	11	5%	5	1%	14	3%	0.064	55	3%
HPV 45 L1	10	3%	12	3%	13	5%	4	2%	9	2%	7	1%	0.076	55	3%
HPV 52 L1	12	3%	13	3%	13	5%	10	5%	10	3%	19	4%	0.511	77	4%
HPV 58 L1	20	5%	17	4%	15	6%	13	6%	26	7%	25	5%	0.854	116	6%
HPV 16 L1 or HPV 18 L1	25	7%	24	6%	24	10%	18	9%	24	6%	26	6%	0.307	141	7%
Number of high risk HPV L1 types															
0 types	300	82%	334	88%	192	77%	170	81%	330	83%	401	85%	0.076	1727	83%
1 type	53	14%	30	8%	39	16%	31	15%	48	12%	47	10%		248	12%
2 types	4	1%	5	1%	6	2%	4	2%	11	3%	10	2%		40	2%
3 types	4	1%	3	1%	3	1%	1	< 1%	6	2%	6	1%		23	1%
4 types	3	1%	4	1%	2	1%	0	0%	1	< 1%	4	1%		14	1%
5 types	2	1%	0	0%	3	1%	1	< 1%	0	0%	2	< 1%		8	< 1%
6 types	0	0%	1	< 1%	1	< 1%	2	1%	0	0%	0	0%		4	< 1%
7 types	2	1%	4	1%	2	1%	1	< 1%	0	0%	1	< 1%		10	< 1%
HPV 16 E6	1	< 1%	4	1%	0	0%	4	2%	0	0%	2	< 1%	**0.019**	11	1%
HPV 16 E7	18	5%	28	7%	14	6%	4	2%	31	8%	24	5%	**0.041**	119	6%
HPV 18 E6	2	1%	2	1%	4	2%	5	2%	5	1%	10	2%	0.174	28	1%
HPV 18 E7	4	1%	3	1%	1	< 1%	0	0%	1	< 1%	3	1%	0.541	12	1%

Abbreviations: HELIUS=HEalthy LIfe in Urban Setting; HPV=human papillomavirus
* *p*-values are based on chi-squared test and significant results ($p < 0.05$) are represented in bold type.
[a] Seropositive for at least one of the following HPV types 16, 18, 31, 33, 45, 52, or 58.

about 50% of them (only the two general questions regarding sex were posed to all, independent of age: 'ever had sex' and LSP). These analyses enabled finer adjustment for sexual risk behaviour. This resulted in two separate models 4: model 4a in which we adjusted for STI test behaviour in the past 6 months and LSP, and model 4b, among participants who reported to ever have had sex, in which (in addition to the determinants used in model 4a) we also adjusted for age of sexual debut and sexual activity in the preceding six months.

This resulted in the following subgroup analyses: (1) men aged 18–44 years excluding MSM, (2) men aged 18–34 years excluding MSM, (3) men aged 18–34 years reporting ever having had sex excluding MSM, (4) men aged 18–34 years, and (5) men aged 18–34 years reporting ever having had sex. We performed, in analogy to the male population, similar subgroup analyses among women.

To confirm if the hrHPV seroprevalence is consistently higher among women compared to men, we used logistic regression models with GEE to investigate the association between gender and hrHPV seropositivity for each ethnicity separately, and in the total study population. We adjusted the association between hrHPV seropositivity and gender for age (model 1), age and sociodemographic determinants (model 2), age, sociodemographic and health related determinants (model 3), and age, sociodemographic and health related and sexual behavioural determinants (model 4). We performed sensitivity analyses in which the association between hrHPV seropositivity and gender was explored among the following subgroups: (1) participants aged 18–34 years, and (2) participants aged 18–34 years reporting ever having had sex.

Statistical analyses were performed using Stata 14 (Stata Intercooled, College Station, TX, USA)[31]. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Baseline characteristics among men by ethnicity

Socio-demographic characteristics differed significantly across ethnicities (Supplementary Table. 1): Dutch men were highest educated, African Surinamese men reported most often to be single, and Dutch men reported most often not to be religious. Dutch, South-Asian Surinamese, and African Surinamese men reported most often not to be circumcised. Ghanaian men reported most often to never have smoked. Although we aimed to randomly select 20 men per life year in each ethnic group, Ghanaian men were older due to a limited number of young Ghanaian men enrolled in HELIUS. Overall, 88% reported to ever have had sex, with African Surinamese men reporting the highest sexual risk behaviour.

3.2. Baseline characteristics among women by ethnicity

Among women, the different ethnic groups also differed significantly from each other (Supplementary Table. 1): Dutch women were highest educated, African Surinamese women reported most often to be single, and Dutch women reported most often not to be religious. Dutch women reported most often to ever have used oral contraceptives. Moroccan women reported most often never having had sex (32%), while Dutch and African Surinamese women reported most often to have had sex (95%). Dutch women, followed by African Surinamese women, reported the highest sexual risk behaviour.

3.3. Baseline characteristics by gender separately for each ethnicity

Socio-demographic characteristics were overall similar between men and women within each ethnicity (statistical test results not shown). Women reported more often never having smoked. More Moroccan ($p < 0.001$) and Turkish ($p=0.006$) men than women within that group reported having had sex. Sexual risk behaviour was overall

Table 2
High-risk HPV seroprevalence among women aged 18–44 years, by ethnicity, the HELIUS study Amsterdam, the Netherlands, January 2011–June 2014.

	Dutch		South-Asian Surinamese		African Surinamese		Ghanaian		Moroccan		Turkish			Total	
	(n=411)		(n=405)		(n=391)		(n=348)		(n=524)		(n=484)		p*	(n=2563)	
	n	%	n	%	n	%	n	%	n	%	n	%		n	%
High risk HPV[a]	125	30%	91	22%	132	34%	109	31%	74	14%	72	15%	**< 0.001**	603	24%
HPV 16 L1	63	15%	47	12%	82	21%	59	17%	23	4%	26	5%	**< 0.001**	300	12%
HPV 18 L1	37	9%	29	7%	68	17%	54	16%	13	2%	19	4%	**< 0.001**	220	9%
HPV 31 L1	57	14%	49	12%	62	16%	41	12%	23	4%	23	5%	**< 0.001**	255	10%
HPV 33 L1	29	7%	19	5%	41	10%	29	8%	12	2%	13	3%	**< 0.001**	143	6%
HPV 45 L1	34	8%	25	6%	57	15%	42	12%	14	3%	15	3%	**< 0.001**	187	7%
HPV 52 L1	35	9%	29	7%	50	13%	39	11%	16	3%	8	2%	**< 0.001**	177	7%
HPV 58 L1	36	9%	34	8%	49	13%	43	12%	27	5%	19	4%	**< 0.001**	208	8%
HPV 16 L1 or HPV 18 L1	78	19%	59	15%	99	25%	74	21%	29	6%	35	7%	**< 0.001**	374	15%
Number of high risk HPV L1 types															
0 types	286	70%	314	78%	259	66%	239	69%	450	86%	412	85%	**< 0.001**	1960	76%
1 type	74	18%	46	11%	52	13%	50	14%	53	10%	46	10%		321	13%
2 types	16	4%	13	3%	25	6%	17	5%	10	2%	12	2%		93	4%
3 types	5	1%	7	2%	8	2%	7	2%	3	1%	8	2%		38	1%
4 types	8	2%	9	2%	8	2%	9	3%	0	0%	4	1%		38	1%
5 types	6	1%	4	1%	8	2%	5	1%	4	1%	0	0%		27	1%
6 types	4	1%	1	< 1%	6	2%	6	2%	2	< 1%	1	< 1%		20	1%
7 types	12	3%	11	3%	25	6%	15	4%	2	< 1%	1	< 1%		66	3%
HPV 16 E6	3	1%	4	1%	4	1%	6	2%	2	< 1%	1	< 1%	0.175	20	1%
HPV 16 E7	16	4%	20	5%	22	6%	8	2%	11	2%	13	3%	**0.020**	90	4%
HPV 18 E6	4	1%	2	< 1%	7	2%	4	1%	9	2%	4	1%	0.429	30	1%
HPV 18 E7	2	< 1%	5	1%	2	1%	3	1%	3	1%	6	1%	0.650	21	1%

Abbreviations: HELIUS=HEalthy LIfe in Urban Setting; HPV=human papillomavirus
* p-values are based on chi-squared test and significant results ($p < 0.05$) are represented in bold type.
[a] Seropositive for at least one of the following HPV types 16, 18, 31, 33, 45, 52, or 58.

higher among men than women, although Dutch men and women were similar except for age of sexual debut (women had significantly younger age of sexual debut).

3.4. Seroprevalence of hrHPV by ethnicity

African Surinamese men had the highest seroprevalence of hrHPV (23%), followed by Ghanaian (19%), Dutch (18%), Moroccan (17%), Turkish (15%), and South-Asian Surinamese men (12%) (p=0.015) (Table 1). When examining the individual hrHPV types, only HPV31 differed across ethnicities. Seropositivity for more than one HPV serotype occurred in around 5% of men.

Among women, hrHPV and individual HPV type seroprevalences differed significantly between ethnicities (Table 2). Seroprevalence of hrHPV was highest among African Surinamese women (34%), followed by Dutch (30%), Ghanaian (31%), South-Asian Surinamese (22%), Turkish (15%), and Moroccan (14%) women ($p < 0.001$). African Surinamese and Ghanaian women were most often seropositive for more than one HPV type.

The seroprevalences of antibodies against early oncoproteins E6 and E7 of both HPV 16 and HPV 18 were low in all ethnicities among both men and women.

3.5. Seroprevalence of hrHPV by age, age of sexual debut, and lifetime number of sexual partners

Among men, the probability for hrHPV seropositivity was not associated with age (p=0.142) (Fig. 1. A), age of sexual debut (p=0.476) (Fig. 1. B), and LSP (p=0.187) (Fig. 1. C). Among women however, the probability to be hrHPV seropositive was high among those with an early sexual debut (up to 20 years of age) and plateaued when the debut was later ($p < 0.001$) (Fig. 1. D); the probability showed a steep linear trend with number of LSP among women ($p < 0.001$) (Fig. 1. E).

As among women the interaction between age and ethnicity was significant, hrHPV seropositivity by age is presented separately for each ethnicity (Fig. 2). Among Dutch women, a relatively flat trend was observed with a small dip between the ages 30–40 years. Only the trends of hrHPV seropositivity by age among Ghanaian and Turkish women differed significantly from the trend observed in Dutch women. Among Ghanaian women, the probability for hrHPV seropositivity was much higher after the age of 30. Among Turkish women the trend was less clear, with a slight increase after the age of 27. This interaction was not significant anymore after correction for sexual behavioural variables.

3.6. Association between ethnicity and hrHPV seroprevalence

Among men there were no significant differences in hrHPV seroprevalence by ethnicity: African-Surinamese men had a non-significant higher hrHPV seroprevalence while the other non-Dutch ethnicities had a non-significant lower hrHPV seroprevalence when compared to Dutch men (Table 3). In Supplementary Table. 3 the results of the different subgroups are presented, which show comparable results.

Among women, African-Surinamese women had a significantly higher odds to be hrHPV seropositive (OR:1.54, 95%CI:1.13–2.09), while Moroccan (OR:0.32, 95%CI:0.21–0.49) and Turkish (OR:0.29, 95%CI:0.19–0.44) women had a significantly lower odds to be hrHPV seropositive than Dutch women (Table 4). After adjustment for socio-demographic, health, and sexual behavioural differences these differences were no longer significant, although the odds to be hrHPV seropositive remained lower among Turkish and Moroccan women. In sensitivity analyses after exclusion of WSW, similar patterns of associations were found (Supplementary Table. 4). In a sensitivity analysis among women aged 18–34 years, Ghanaian women had overall lower odds to be hrHPV seropositive.

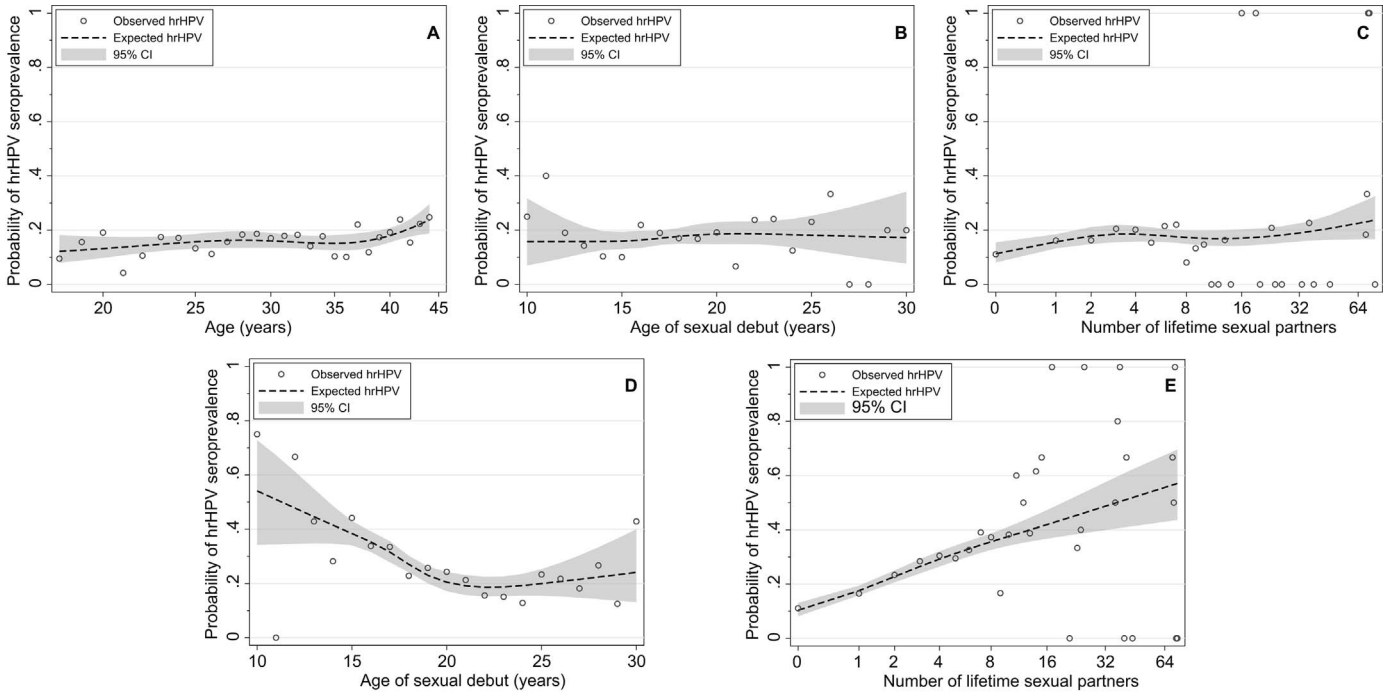

Fig. 1. Estimated probability of high risk HPV seroprevalence, for all ethnicities together, in men as a function of (A) age, (B) age of sexual debut, and (C) lifetime number of sexual partners, and in women as a function of (D) age of sexual debut and (E) lifetime number of sexual partners. Among men, the association between age (p=0.142), age of sexual debut (p=0.467) and lifetime number of sexual partners (p=0.187) with hrHPV seropositivity was not significant. Among women, the association of age of sexual debut ($p < 0.001$) and lifetime number of sexual partners ($p < 0.001$) with hrHPV seropositivity was significant. There was no significant interaction between age (p=0.429 among men), age of sexual debut (p=0.817 among men, p=0.502 among women) and lifetime number of sexual partners (p=0.423, p=0.169 among women) with ethnicity. *P*-values presented are based on logistic regression using generalised estimating equation. Expected high risk HPV prevalence was derived from a 4-knot restricted cubic spline standard logistic regression model using default knot values (dashed line). The grey shading depicts the 95% confidence interval for expected high risk seroprevalences. Dots represent the observed seroprevalence of hrHPV.

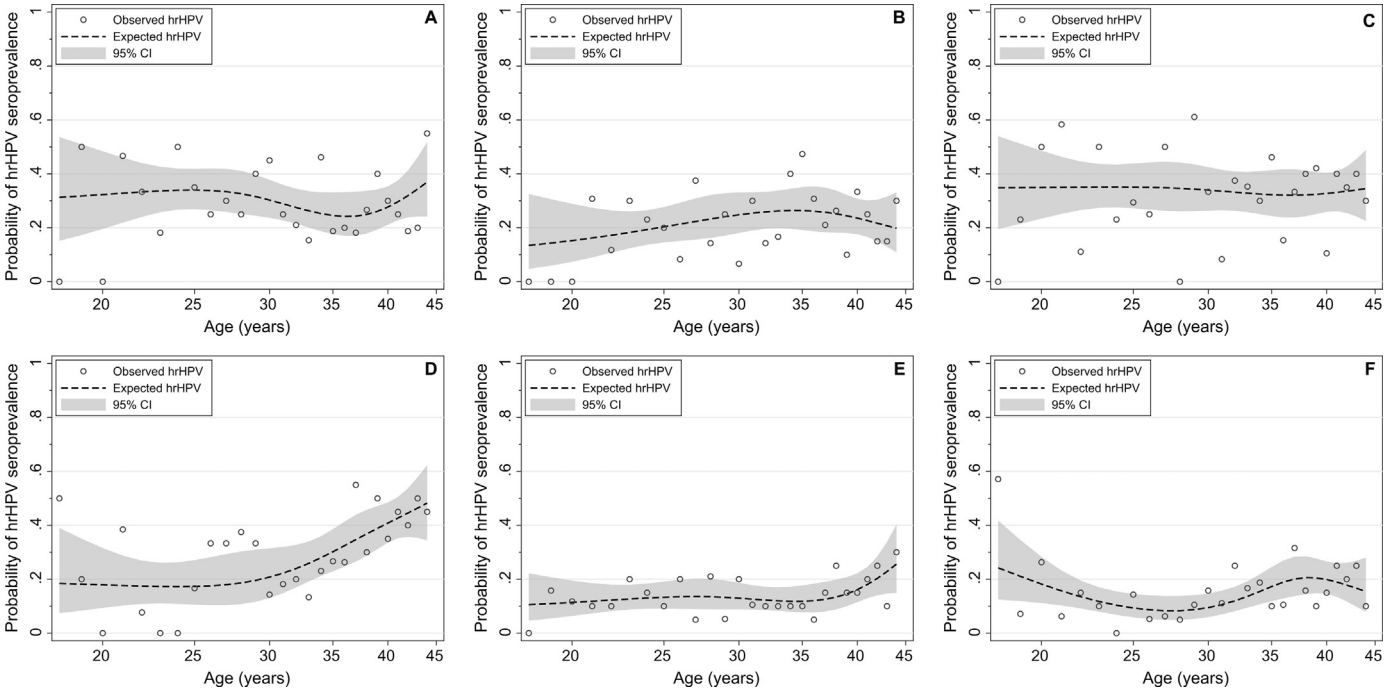

Fig. 2. Estimated probability of high-risk HPV seroprevalence among women as a function of age are presented separately for (A) Dutch (p=0.329), (B) South-Asian Surinamese (p=0.925), (C) African Surinamese (p=0.279), (D) Ghanaian (p=0.011), (E) Moroccan (p=0.710) and (F) Turkish women (p=0.030). *P*-value presented within parentheses are based on logistic regression using generalised estimating equation and represents the strength of association between age and hrHPV seropositivity as outcome. Estimated probabilities of high-risk HPV seropositivity as a function of age are presented separately for all ethnicities because of significant interaction between age and ethnicity with hrHPV seropositivity as outcome (p-interaction=0.100). Expected high risk HPV prevalence is derived from a 4-knot restricted cubic spline standard logistic regression model using default knot values (dashed line). The grey shading depicts the 95% confidence interval for expected high risk HPV seroprevalences. Dots represent the observed seroprevalence of hrHPV per age-year.

Table 3
Association between ethnicity and high-risk human papillomavirus using logistic regression with generalised estimating equations among men aged between 18 and 44 years, the HELIUS study Amsterdam, the Netherlands, January 2011–June 2014.

	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Men aged 18–44 years (n=1844)[a]								
	Model 1		**Model 2**		**Model 3**		**Model 4**	
Dutch	1		1		1		1	
South-Asian Surinamese	0.88	(0.56–1.38)	1.06	(0.63–1.77)	0.95	(0.57–1.61)	0.99	(0.59–1.67)
African Surinamese	1.39	(0.88–2.21)	1.61	(0.96–2.70)	1.51	(0.90–2.54)	1.40	(0.83–2.38)
Ghanaian	0.91	(0.53–1.58)	1.13	(0.61–2.12)	0.76	(0.37–1.56)	0.75	(0.36–1.56)
Moroccan	0.77	(0.48–1.24)	1.02	(0.56–1.85)	0.69	(0.35–1.37)	0.74	(0.37–1.47)
Turkish	0.81	(0.52–1.28)	1.04	(0.59–1.83)	0.72	(0.38–1.39)	0.78	(0.40–1.51)

Multivariable models are adjusted for the following risk factors:
Model 1: age
Model 2: model 1+ marital status, education and religion
Model 3: model 2+ smoking status and circumcision status
Model 4: model 3+ STI test behaviour during preceding six months and lifetime number of sexual partners
For analytic purposes continuous variables (age and lifetime number of sexual partners) were modelled using restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentile. Lifetime number of sexual partners was log transformed. Marital status was categorized into '(ever) married' and 'single'. Education was categorized into 'lower', 'intermediate' and 'higher' education. Religion was dichotomized into 'not religious' and 'religious'. Smoking status was categorized into 'never', ' < 2 pack years' and '≥2 pack years'. Circumcision status was categorized into 'not circumcised' and 'circumcised'.
Significant results ($p < 0.05$) are represented in bold type.
Abbreviations: HELIUS=Healthy Life in Urban Setting; hrHPV=high-risk human papillomavirus; STI=sexually transmitted infection; aOR=adjusted Odds Ratio; 95% CI=95% Confidence Interval
[a] Analyses of models 1 through 4 are based on subjects with complete data, and are based on the same risk set. Therefore the number of included men is 1844 rather than 2074.

3.7. Association between gender and hrHPV seropositivity

Women consistently had significantly higher odds than men to be hrHPV seropositive, among all ethnic groups, except in the Moroccan and Turkish groups (Table 5). In these two groups the odds to be hrHPV seropositive was similar among men and women. To allow for finer adjustment of sexual behavioural differences, sensitivity analyses among participants aged 18–34 years were executed (Supplementary Table. 5). After adjustment for sexual behavioural characteristics, Moroccan women had a significant higher odds to be hrHPV seropositive compared to Moroccan men, while Turkish women continued to have a similar (models 4a and model 4b, Supplementary Table. 5) odds to be hrHPV seropositive when compared to Turkish men.

4. Discussion

Among men we observed an overall low hrHPV seroprevalence that was not significantly different when comparing non-Dutch men to Dutch men. Among women we found pronounced variations across ethnic groups, with a higher hrHPV seroprevalence among African Surinamese and lower hrHPV seroprevalence among Moroccan and Turkish women when compared to Dutch women. All these variations could be explained by differences in demographic (age, education, marital status and religion), health (smoking, circumcision status [among men] and oral contraceptive use [among women]), and sexual (e.g. STI [including HIV] test behaviour in the past 6 months, LSP, age of sexual debut and sexual activity in the preceding six months)

Table 4
Association between ethnicity and high-risk human papillomavirus using logistic regression with generalised estimating equations among women aged between 18 and 44 years, the HELIUS study Amsterdam, the Netherlands, Jan. 2011–Jun. 2014.

	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Women aged 18–44 years (n=2385)[a]								
	Model 1		**Model 2**		**Model 3**		**Model 4**	
Dutch	1		1		1		1	
South-Asian Surinamese	0.79	(0.57–1.11)	0.72	(0.48–1.08)	0.76	(0.51–1.14)	1.18	(0.78–1.79)
African Surinamese	**1.54**	**(1.13–2.09)**	1.25	(0.86–1.81)	1.21	(0.83–1.77)	1.30	(0.89–1.90)
Ghanaian	1.05	(0.74–1.49)	0.89	(0.57–1.39)	1.07	(0.67–1.71)	1.34	(0.84–2.14)
Moroccan	**0.29**	**(0.19–0.44)**	**0.28**	**(0.17–0.46)**	**0.33**	**(0.20–0.55)**	0.64	(0.38–1.07)
Turkish	**0.32**	**(0.21–0.49)**	**0.32**	**(0.19–0.52)**	**0.37**	**(0.23–0.61)**	0.79	(0.47–1.33)

Multivariable models are adjusted for the following risk factors:
Model 1: age
Model 2: model 1+ marital status, education and religion
Model 3: model 2+ smoking status and oral contraceptive use
Model 4: model 3+ STI test behaviour during preceding six months and lifetime number of sexual partners
For analytic purposes continuous variables (age and lifetime number of sexual partners) were modelled using restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentile. Lifetime number of sexual partners was log transformed. Marital status was categorized into '(ever) married' and 'single'. Education was categorized into 'lower', 'intermediate' and 'higher' education. Religion was dichotomized into 'not religious' and 'religious'. Smoking status was categorized into 'never', ' < 2 pack years' and '≥2 pack years'. Oral contraceptive use dichotomized into 'no'/'yes'.
Significant results ($p < 0.05$) are represented in bold type.
Please note that in this model we did not account for interaction between age and ethnicity, which was significant among women.
Abbreviations: HELIUS=Healthy Life in Urban Setting; hrHPV=high-risk human papillomavirus; STI=sexually transmitted infection; aOR=adjusted Odds Ratio; 95% CI=95% Confidence Interval
[a] Analyses of models 1 through 4 are based on subjects with complete data, and are based on the same risk set. Therefore the number of included women is 2385 rather than 2563.

Table 5
Association between gender and high-risk human papillomavirus using logistic regression with generalised estimating equations among participants aged between 18 and 44 years, the HELIUS study Amsterdam, the Netherlands, January 2011–June 2014[a].

	Model 1		Model 2		Model 3		Model 4	
	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Total study population aged 18–44 years (n=4252)								
Men	1		1		1		1	
Women	**2.03**	**(1.70–2.43)**	**2.09**	**(1.74–2.50)**	**2.09**	**(1.74–2.50)**	**2.66**	**(2.18–3.25)**
Dutch aged 18–44 years (n=756)								
Men	1		1		1		1	
Women	**2.37**	**(1.59–3.53)**	**2.44**	**(1.64–3.64)**	**2.43**	**(1.64–3.61)**	**2.67**	**(1.80–3.96)**
South-Asian Surinamese aged 18–44 years (n=746)								
Men	1		1		1		1	
Women	**2.38**	**(1.50–3.79)**	**2.33**	**(1.48–3.67)**	**2.37**	**(1.49–3.78)**	**3.70**	**(2.20–6.20)**
African Surinamese aged 18–44 years (n=593)								
Men	1		1		1		1	
Women	**2.95**	**(1.87–4.63)**	**3.23**	**(2.04–5.11)**	**3.31**	**(2.10–5.22)**	**3.52**	**(2.12–5.86)**
Ghanaian aged 18–44 years (n=461)								
Men	1		1		1		1	
Women	**2.91**	**(1.64–5.16)**	**2.96**	**(1.67–5.25)**	**2.89**	**(1.64–5.10)**	**3.80**	**(2.01–7.16)**
Moroccan aged 18–44 years (n=852)								
Men	1		1		1		1	
Women	0.99	(0.63–1.55)	0.97	(0.62–1.52)	1.21	(0.74–1.98)	1.29	(0.77–2.17)
Turkish aged 18–44 years (n=844)								
Men	1		1		1		1	
Women	1.00	(0.65–1.53)	1.03	(0.67–1.57)	0.97	(0.63–1.50)	1.18	(0.72–1.94)

Multivariable models are adjusted for the following risk factors:
Model 1: age (and ethnicity in the total study population)
Model 2: model 1+ marital status, education and religion
Model 3: model 2+ smoking status
Model 4: model 3+ STI test behaviour during preceding six months and lifetime number of sexual partners
For analytic purposes continuous variables (age and lifetime number of sexual partners) were modelled using restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentile. Lifetime number of sexual partners was log transformed. Lifetime number of sexual partners was log transformed. Marital status was categorized into '(ever) married' and 'single'. Education was categorized into 'lower', 'intermediate' and 'higher' education. Religion was dichotomized into 'not religious' and 'religious'. Smoking status was categorized into 'never', '< 2 pack years' and '≥2 pack years'.
Significant results ($p < 0.05$) are represented in bold type.
Abbreviations: HELIUS=Healthy Life in Urban Setting; hrHPV=high-risk human papillomavirus; STI=sexually transmitted infection; aOR=adjusted Odds Ratio; 95% CI=95% Confidence Interval
[a] Analyses of models 1 through 4 are based on subjects with complete data, and are based on the same risk set.

behavioural differences between ethnicities. We confirm that hrHPV seroprevalence is significantly higher among women when compared to men, except for the Turkish group. Finally, among individuals of the general population in Amsterdam, the seroprevalence of antibodies against early oncoproteins E6 and E7 of both HPV 16 and HPV 18 (predictors of oropharyngeal and anal cancer [32–34]) was as expected very low in all ethnicities among both men and women.

As reported in previous studies, no clear trend in hrHPV seropositivity by age [35,36], age of sexual debut [26], or LSP [26,30,35,36] was observed among men. Our data suggest that men –despite being exposed to HPV– do not develop antibodies readily, as the probability to be hrHPV seropositive only increased slightly with increasing number of LSP. Furthermore, previous studies have shown that site of exposure (vaginal/cervical, penile, oral, or anal) influences the probability of seroconversion; as a consequence, heterosexual men have overall lower HPV seroprevalences than women [25,26,37]. When relating our results (no strong relation between hrHPV seropositivity with age, age of sexual debut, and lifetime number of sexual partners among men) with the lower HPV seroprevalence found among heterosexual men, we may conclude that HPV serology is not a useful indicator of sexual exposure or past HPV infection among men of the general population.

Among women, the typical pattern as described in the literature for HPV seroprevalence by age is an increase in probability of hrHPV seropositivity with increasing age up to 20–25 years, and a decreasing probability after the age of 40–50 years [38–40]. It is possible that we did not observe clear trends between hrHPV seropositivity and age because of the limited age range under investigation, i.e. 18–44 years old. However, the slight trends observed indicated an increase in hrHPV seropositivity by age starting at different ages among Dutch (~40 years), Ghanaian (~30 years), and Moroccan (~35 years) women, while among African Surinamese participants hrHPV seropositivity did not change by age. The pattern found among South-Asian Surinamese women was similar to that described in the literature [38–40]. Among women, a sexual debut at a young age was associated with hrHPV seropositivity. Furthermore, we found that the probability to be hrHPV seropositive among women increased linearly with the log of the LSP, as observed previously [38].

We confirm that hrHPV seroprevalence is higher among women than among men after adjustment for differences in sexual behaviour [24–26], except for Turkish women. It is very well plausible that the statistical model used was not able to fully account for differences in sexual risk behaviour in the Turkish group and that the lower seroprevalence observed among these groups can be accounted to the lower exposure to HPV infections among Turkish women (when compared to Dutch women [age adjusted OR: 0.32, 95%CI:0.21–0.49] and when compared to men [age adjusted OR: 1.00, 95% CI:0.65–1.53]; we expected this last association to be well above 1 as it is known that women have a higher HPV seroprevalence than heterosexual men [25,26,37]). It is also possible that Turkish women do not develop antibodies against HPV as easily as women from other ethnicities.

This is one of the first studies to compare hrHPV seroprevalence between different ethnicities separately for men and women from the general population. A strength of this study is that ethnicity was based on the country of birth of both of the parents rather than on self-identified ethnicity or race (except for the Surinamese subgroups) [27,28]. An important limitation of this study is that HIV was not measured although it is a well-known risk factor for HPV seropositivity [41]. This study concerns an ethnically diverse cohort, for which trust and support from the community is needed to successfully recruit enough participants. Community leaders voiced the concern that HIV testing could undermine the trust of participants; therefore it was decided not to test for HIV. We do not expect this to have had an important influence on our results, as HIV prevalences are estimated to be very low in the general population (< 0.5%) [42], and are estimated to be similarly low in each of the ethnic groups included in this study [43].

As mentioned previously we found that HPV was not a good marker for past HPV infection or sexual exposure among men. Although it is known that not every person develops antibodies against a prevalent HPV infection [44,45], we found in a smaller study sample embedded in this larger cohort that current infection with hrHPV (as determined by HPV DNA detection) is significantly associated with hrHPV seropositivity among women [46]. Finally, within this same smaller study sample we found a different distribution of hrHPV infection across ethnicities in women [21]. Thus, it will be most likely worth-

while to also compare hrHPV infection distributions between ethnicities among men.

5. Conclusions

In conclusion, among men no clear trend of hrHPV seropositivity was observed with age, age of sexual debut, and LSP. This may explain why no significant differences across ethnicities among men were observed and implies that HPV seropositivity is not a good marker for past sexual exposure among men of the general population, while among women it is. We furthermore conclude that differences in hrHPV seropositivity across ethnicities among women could largely be explained by demographic, health and sexual behaviour differences. Finally, our results confirm that women have higher hrHPV seroprevalences than men, except in the Turkish group.

Conflict of interest statement

M.F. Schim van der Loeff received research funding from Sanofi Pasteur MSD; he is a co-investigator in a Merck-funded investigator-initiated study on Gardasil; he is an investigator on a Sanofi Pasteur MSD sponsored HPV vaccine trial; he served on a vaccine advisory board of GSK; he received in-kind contribution for another study from Stichting Pathologie Onderzoek en Ontwikkeling (SPOO); his institution receives research funding from Janssen Infectious Diseases and Vaccines; other authors: no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pvr.2017.01.003.

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