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Review

Human papillomavirus vaccination and the risk of autoimmune disorders: A systematic review and meta-analysis

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ABSTRACT

Introduction: Human papillomavirus (HPV) vaccination has been proven to effectively protect against HPV infection and infection-associated cancer. However, there are concerns about the relationship between HPV vaccination and the risk of autoimmune disorders (ADs). Therefore, we performed a systematic review and meta-analysis to comprehensively evaluate the relationship between HPV vaccination and ADs risk.

Methods: To identify relevant studies, we conducted a systematic search in EMBASE and PubMed databases of scientific articles published through June 2018. Fixed or random effects models were adopted to estimate overall relative risk.

Results: In total, 20 studies (12 cohort studies, 6 case-control studies, and 2 randomized controlled trials) involving more than 169,000 AD events were included in our meta-analysis. Our results show that HPV vaccination was not associated with an increased risk of subsequent ADs (odds ratio [OR] = 1.003, 95% confidence interval (CI): 0.95–1.06), particularly among those with a prior ADs (OR = 0.82, 95% CI: 0.7–0.96). Most of the subgroup analysis results based on the location or type of ADs were consistent with the overall results.

Conclusion: No evidence of an association between HPV vaccination and ADs was found. Given the low number of estimates for individual AD, additional and larger observational studies are needed to verify our findings.

Contents

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1. Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted infections worldwide, affecting 50–70% of sexually active individuals [1]. About 70% of cervical cancers and 90% of anal cancers are caused by HPV types 16 and 18 [2]. HPV is also responsible for most rare oropharyngeal, vulval, vaginal, and penile cancers [3,4]. Vaccines have been proven to effectively protect against these HPV types, presenting an opportunity to reduce the burden of cervical cancer and other HPV-associated cancers. Since 2006, HPV vaccines have been introduced for female adolescents aged 9–14 years, with a possible application to adult women. More recently, the HPV vaccination of boys has been included in the childhood vaccination schedule in a few countries.

While proven effective, the recommended population coverage has not been achieved in some settings. One possible reason is the concern about a possible link between this vaccination and the occurrence of autoimmune disorders (ADs), notably central demyelinating diseases [5,6]. This suspicion stemmed from case reports of autoimmune events occurring early after HPV vaccination [7–9]. The coverage of HPV vaccination dropped to a low level in many countries after this suspicion spread in the social media and was caught by the media [10,11].

Regardless of global interest in the topic, the latest systematic review focused on the association between HPV vaccination and demyelinating diseases. A meta-analysis of the eleven included studies strongly supported the absence of an association between HPV vaccines and central demyelination [12]. However, several case reports of ADs beyond the central neural system following HPV vaccination were recently reported in the literature [13–16], indicating that HPV vaccines might be causal factors of these disorders. There were also a number of epidemiological studies of the association between HPV vaccination and AD risk, but they reported conflicting findings [17–20]. Some studies [17,19] found no link between HPV vaccine and the risk of ADs. However, several cohort studies [18,20] revealed that HPV vaccination was associated with increased risks of Hashimoto's thyroiditis and coeliac disease. Thus, there is no definite conclusion about the relationship between HPV vaccination and autoimmune disorder risk. Given the concerns above, the aim of this study was to perform a systematic review and meta-analysis to quantitatively assess the available data from studies undertaken in different countries regarding the association between HPV vaccines and ADs.

2. Methods

2.1. Search strategy

A systematic review and meta-analysis was performed in accordance with the guidelines developed by the Meta-analysis of Observational Studies in Epidemiology group [21] (Table S1). A comprehensive search of PubMed and EMBASE from inception to June 2018 was conducted for peer-reviewed studies published in English. Synonymous terms were used to develop the search strategy (Appendix 1). Additionally, reference lists of the retrieved articles and relevant reviews were checked to find additional studies.

2.2. Study selection

Eligibility criteria were defined according to the Participants, Interventions, Comparators, Outcomes, and Study approach. We included observational studies and randomised controlled trials (RCTs) that met all of the following inclusion criteria: (1) case-control, cohort study, or RCT design; (2) HPV vaccination exposure; (3) controls were individuals who did not receive an HPV vaccination; (4) the outcome of interest was the risk for ADs associated with HPV vaccination; (5) reported either a risk ratio (RR), hazard ratio (HR), odds ratio (OR), or incidence rate ratio (IRR) with 95% confidence intervals (CIs). We excluded case reports and series, animal studies, editorials, and reviews. We also excluded studies involving fewer than 50 AD cases.

2.3. Data extraction and quality assessment

Two authors extracted data independently from the included studies using an electronic structured extraction form, and discrepancies were resolved by a third author. The following information was extracted in standardised form: first author's name, year of publication, country, study design, study period, length of follow-up, participant characteristics, measurement of ADs, and confounding factors used for adjustment analysis. Study-specific ORs, RRs, HRs, and IRRs with 95% CIs are presented in Table S2. We assessed the methodologic quality of the included observational studies based on the Newcastle-Ottawa Scale (NOS) as recommended by the Cochrane Collaboration, which was developed to assess the quality of nonrandomised studies in meta-analyses [22] (Tables S3 and S4). A score >7 points was suggestive of a high-quality study. RCTs were classified as high-quality studies.

2.4. Outcome assessment

The analysis focused on assessing the risk of autoimmune diseases among people exposed to HPV vaccination in comparison with those who had not been exposed. Our overall AD risk analysis included only studies that provided estimates for more than 10 kinds of AD if the overall AD risk was not available; these estimates of individual ADs were pooled to give the overall AD risk. To investigate potential sources of heterogeneity, the subgroup analyses were stratified using the following parameters: study design, HPV vaccine type, autoimmune disorder location, autoimmune disorder type, follow-up period, and vaccine recipient age (Table 2). We also performed a post hoc sensitivity analysis by omitting

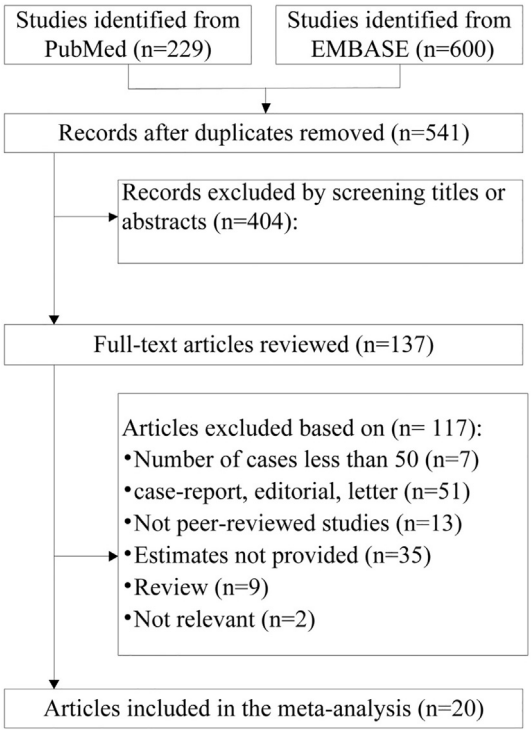

Fig. 1. Flow chart of the studies considered and finally selected for review.

one study at a time. We analysed the location of ADs according to seven broad categories: (1) neurological, (2) thyroid, (3) gastrointestinal, (4) musculoskeletal or systemic, (5) haematological, (6) dermatological, and (7) others.

2.5. Data analysis

Analyses were performed if at least three risk estimates evaluating the same outcome could be combined. If only one or two studies investigated the same outcome, the risk estimates were categorised into other ADs. Pooled results were expressed as the OR of ADs with HPV vaccination compared with no vaccination. ORs were considered approximations of RRs, HRs, or IRRs because the outcome under the study is rare in all populations and subgroups under review [23]. When possible, we extracted adjusted effect estimates between outcome measures and exposure to HPV vaccination with the standard error; otherwise, we calculated the unadjusted risk ratio using the raw data. Heterogeneity was quantified with Cochran's Q and I^2 statistics, with I^2 values <30%, 30–50%, and >50% judged to represent little, moderate, and substantial heterogeneity, respectively [24]. In the presence of substantial heterogeneity, we used a random effects model because its assumptions account for the presence of variability among studies; otherwise, a fixed effects model was used. All analyses were performed using STATA 10.0 (StataCorp, College Station, TX, USA).

3. Results

3.1. Search results

Fig. 1 shows the search process details and study selection along with the reasons for exclusion. In total, 541 potential eligible articles were identified from the initial search after duplicates were excluded. Of these, 461 articles were discarded after reading the titles and abstracts, and the remaining 80 articles were retrieved for detailed assessment. Ultimately, 20 studies [17–20,25–40] met our inclusion criteria and were included in the meta-analysis.

3.2. Descriptive characteristics of the included studies

Table 1 shows the main characteristics of the included studies. Twelve studies were cohort studies, five were case-control studies, one was a self-controlled case series, and two were pooled analyses of RCTs. The 20 studies were published between 2008 and 2018. Among the 20 studies, 6 assessed the association between HPV vaccines and risk for neurological ADs, and 14 assessed the association between HPV vaccines and risk for several autoimmune disorder types. Deceuninck et al. [39] and Andrews et al. [35] analysed only the impact of the HPV vaccine on the risk of Guillain–Barré syndrome, while Sridhar et al. [38] and Baxter et al. [31] assessed only the risk of optic neuritis. Only five studies included male participants, and only one study focused on male participants.

Based on the methodological quality assessment scores, 15 studies were deemed to be of high quality and 5 were categorised as low quality. The score breakdown is given in Tables S3 and S4.

3.3. Overall ADs

A meta-analysis of twelve studies assessing the risk of all ADs in relation to HPV vaccination indicated that the combined OR of autoimmune disorder risk was 1.003 (95% CI: 0.95–1.06) (Fig. 2). Significant heterogeneity was observed among the studies ($I2 = 54.2\%$, $P < 0.001$). When studies were grouped by study design, no significant associations were observed in case-control studies (OR = 0.69, 95% CI: 0.45, 1.04), cohort studies (OR = 1.01, 95% CI: 0.96, 1.07), or RCTs (OR = 0.91, 95% CI: 0.73, 1.15). The sensitivity analysis showed no substantial change in the pooled risk estimates upon the exclusion of any single study. In addition, the exclusion of the three studies that enrolled male participants did not alter the overall result.

Three studies were eligible for the analysis of the risk of new ADs among participants with a history of ADs. The combined OR for new ADs was 0.82 (95% CI: 0.7–0.96). Six studies included only participants under 18 years of age, and the pooled OR (OR = 1.01, 95% CI: 0.95, 1.06) demonstrated no increased risk of ADs among these HPV vaccine recipients.

3.4. Neurological ADs

Nineteen studies reported the risk of neurological ADs in relation to HPV vaccination, and the combined OR of neurological ADs was 0.93 (95% CI: 0.81–1.06) (Fig. S1). Analyses taking into account the type of neurological ADs showed that HPV vaccination was not associated with increased risk of Bell's palsy (OR = 0.86, 95% CI: 0.6, 1.24), epilepsy (OR = 0.9, 95% CI: 0.6, 1.33), Guillain-Barré syndrome (OR = 1.28, 95% CI: 0.65, 2.52), multiple sclerosis (OR = 0.92, 95% CI: 0.56, 1.53), narcolepsy (OR = 1.18, 95% CI: 0.79, 1.74), optic neuritis (OR = 1.12, 95% CI: 0.7, 1.8), paralysis (OR = 0.7, 95% CI: 0.51, 0.95), or other neurological ADs (OR = 0.91, 95% CI: 0.76, 1.1) (Fig. S2).

3.5. Thyroid ADs

Twelve studies reported the risk of thyroid ADs in relation to HPV vaccination, and the combined OR of thyroid ADs was 1.02 (95% CI: 0.92–1.13) (Fig. S3). With respect to the type of thyroid ADs, a significantly increased risk of Hashimoto's thyroiditis associated with HPV vaccination was observed (OR = 1.22, 95% CI: 1.09, 1.36), but not for Grave's disease (OR = 0.94, 95% CI: 0.71, 1.23), hypothyroidism (OR = 0.89, 95% CI: 0.81, 0.98), or hyperthyroidism (OR = 1.03, 95% CI: 0.88, 1.2) (Fig. S4).

Table 1
Characteristics of studies included in the meta-analysis.

Study, year	Country	Study design/Study period	Follow-up time	Sex	Age	Number of events/ Vaccinated	Number of events/ Unvaccinated	Autoimmune disorder measurement	Confounding factors or matched factors	Quality
Verstraeten et al. [25]	Analysis of 16 studies on HPV 16/18 (Cervarix)	RCTs (2007)	1.8 years	F and M	10–87	191/36,744	171/31,768	Medical Dictionary for Regulatory Activities (MedDRA) preferred terms	No	High
Chao et al. [20]	USA	Cohort study (KPSC and KPNC) (2006–2008)	6 months	F	9–26	156/117761	986/412151	ICD-9	No	Low
Arnheim-Dahlstrom et al. [26]	Denmark and Sweden	Nationwide cohorts (2006–2010)	6 months	F	10–17	1043/296826	11939/700759	ICD-10	country, age in two-year categories, calendar year, parental educational level;, parental country of birth, and paternal socioeconomic status	High
Angelo et al. [27]	Analysis of 42 studies on HPV 16/18 (Cervarix)	RCTs (2011)	30 days	F	9–72	97/21358	50/20504	Medical Dictionary for Regulatory Activities (MedDRA) preferred terms	No	High
Grimaldi-Bensouda et al. [28]	France	Case-control (PGRx) (2006–2011)	2 months for GBS; 6 months for ITP; 24 months for other autoimmune disorders	F	14–16	211 cases	875 controls	Internationally accepted classifications	age, familial/personal history of autoimmune disease, parents' place of birth, and use of any oral contraceptives or vaccines (other than human papillomavirus vaccine) within 2 years before index date.	Low
Langer-Gould et al. [29]	USA	Nest case-control (KPSC) (2007–2011)	3 years	F and M	39.3	780 cases	3885 controls	ICD-9	race/ethnicity, hospitalizations, outpatient visits, emergency department visits, comorbid chronic diseases, and infections within 6 months before symptom onset/ index date	High
Scheller et al. [30]	Denmark and Sweden	Nationwide cohorts (2006–2013)	2 years	F	10–44	163/1193703	7362/19546190	ICD-10	calendar year, age (2-year intervals), and country	High
Baxter et al. [31]	USA	Case-centered analysis in KPNC (2007–2012)	42 days	F and M	NR	91/NR	NR/NR	diagnosis made by either an ophthalmologist or a neurologist within 3 months of initial diagnosis. Trained medical records analysts reviewed all identified cases to verify the specialist diagnosis	age, sex, and vaccine type	High
Gronlund et al. [32]	Sweden	Cohort study (2006–2012)	6 months	F	10–30	124/11256	5248/59009	ICD-10	country of birth, parental country of birth, parental income and parental education	High
Lehtinen et al. [33]	Finland	Cohort study (2007–2010)	12 months	F and M	12–16	81/14838	141/17338	ICD-10	No	Low
Willame et al. [34]	UK	Cohort study (2008–2010)	1 year	F	9–25	42/64705	39/64841	pre-defined algorithms	age	High
Andrews et al. [35]	England	self-controlled case-series (2007–2016)	3 months	F	12–18	101 cases	NR/NR	ICD-10	age, period and season	High
Geier et al. [40]	USA	Case-control (VAERS) (2006–2014)	NA	F	6–39	228/15367	348/33463	VAERS code	No	Low

Table 1 (*continued*)

Study, year	Country	Study design/Study period	Follow-up time	Sex	Age	Number of events/ Vaccinated	Number of events/ Unvaccinated	Autoimmune disorder measurement	Confounding factors or matched factors	Quality
Grimaldi-Bensouda et al. [36]	French	prospective case-referent (PGRx) (2008–2014)	2 months for GBS; 6 months for ITP; 24 months for other autoimmune disorders	F	11–25	510 cases	1953 controls	Chart Review	age, familial/personal history of autoimmune disease, parent's place of birth, and use of any oral contraceptives or vaccines (other than human papillomavirus vaccine) within 2 years before the index date	High
Miranda et al. [37]	French	Cohort study (2008–2012)	33 months	F	13–16	1020/842120	3879/1410596	Chart Review	age (time scale), year of inclusion, geographical zone, history of use of health care and other vaccinations, use of health care and other vaccinations after inclusion	High
Sridhar et al. [38]	USA	Cohort study (HIRD) (2007–2012)	60 days	F	9–26	36/327,918	32/327,918	medical chart review	History of other autoimmune diseases, other vaccinations, enhanced deyo-Charlson index, region	High
Deceuninck et al. [39]	Canada	Cohort study (1999–2014)	NR	F	9–17	100/NR	NR	medical chart review	sex, age, year of diagnosis, and H1N1 pandemic period	Low
Frisch et al. [19]	Denmark	Cohort study (2006–2016)	11.8 years	M	10–17	46/7384	7985/561026	ICD-10	age and calendar year	High
Hviid et al. [18]	Denmark and Sweden	Cohort study (2006–2013)	2.7 years	F	18–44	123739/2876647	2014/250143	ICD-10	age, calendar period and country of residence	High
Liu et al. [17]	Canada	Cohort study (2007–2013)	2.9 years	F	12–17	77/99 841	604/825 160	diagnostic codes with clinical experts	age at diagnosis, seasonality, receipt of non-HPV vaccines and recent infection	High

F, female; HPV, human papillomavirus vaccination; HIRD, Health Core's Integrated Research Database; ICD, International Statistical Classification of Diseases; M, male; NR, not reported; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California; PGRx, Pharmacoepidemiologic General Research Extension; RCT, randomized-controlled trial; VAERS, vaccine adverse event reporting system.

Table 2
Subgroup analysis for studies included in the analysis.

Subgroup analysis	Number of studies	Number of estimates	Pooled OR (95% CI), I^2 statistics (%), P-value for the heterogeneity Q test	Model used
Overall autoimmune disorders	12	114	1.003 (0.95–1.06); I^2 = 54.2%, P < 0.001	Random effect
Participants with a history of autoimmune disorder	3	3	0.82 (0.7–0.96); I^2 = 26.8%, P = 0.26	Fixed effect
Participants under 18 years old	6	56	1.01 (0.95–1.06); I^2 = 32.6%, P = 0.01	Fixed effect
Study design				
Case-control	2	2	0.69 (0.45–1.04); I^2 = 42.5%, P = 0.04	Fixed effect
Cohort	8	110	1.01 (0.96–1.07); I^2 = 54%, P < 0.001	Random effect
RCT	2	2	0.91 (0.72–1.15); I^2 = 0%, P = 0.93	Fixed effect
Neurological	19	35	0.93 (0.91–1.06); I^2 = 60.7%, P < 0.001	Random effect
Bell's palsy	4	4	0.86 (0.6–1.24); I^2 = 60%, P = 0.057	Random effect
Epilepsy	3	3	0.9 (0.6–1.33); I^2 = 83.4%, P < 0.001	Random effect
Guillain-Barré syndrome	4	4	1.28 (0.65–2.52); I^2 = 77%, P = 0.004	Random effect
Multiple sclerosis	5	5	0.92 (0.56–1.53); I^2 = 0%, P = 0.563	Random effect
Narcolepsy	4	4	1.18 (0.79–1.74); I^2 = 0%, P = 0.502	Fixed effect
Optic neuritis	6	6	1.12 (0.7–1.8); I^2 = 55.2%, P = 0.048	Random effect
Paralysis	3	3	0.7 (0.51–0.95); I^2 = 19.9%, P = 0.287	Fixed effect
Others	4	6	0.91 (0.76–1.1); I^2 = 40.3%, P = 0.137	Fixed effect
Thyroid	12	22	1.02 (0.91–1.14); I^2 = 55.3%, P = 0.001	Random effect
Hashimoto's thyroiditis	10	10	1.22 (1.09–1.36); I^2 = 0%, P = 0.566	Fixed effect
Grave's disease	5	5	0.94 (0.71–1.23); I^2 = 51%, P = 0.09	Random effect
Hypothyroidism	4	4	0.89 (0.81–0.98); I^2 = 0%, P = 0.567	Fixed effect
Hyperthyroidism	3	3	1.03 (0.88–1.2); I^2 = 98.6%, P < 0.007	Fixed effect
Gatrointestinal	10	25	1.06 (0.99–1.14); I^2 = 42.6%, P = 0.013	Fixed effect
Inflammatory bowel diseases	9	15	1.05 (0.97–1.14); I^2 = 12.5%, P = 0.313	Fixed effect
Crohn's disease	7	7	1 (0.86–1.16); I^2 = 0%, P = 0.683	Fixed effect
Ulcerative colitis	8	8	1.01 (0.88–1.15); I^2 = 25.6%, P = 0.225	Fixed effect
Celiac disease	7	7	1.12 (0.85–1.47); I^2 = 51.4%, P = 0.055	Random effect
Pancreatitis	3	3	0.88 (0.73–1.06); I^2 = 0%, P = 0.66	Fixed effect
Musculoskeletal or systemic	12	47	1.07 (0.98–1.17); I^2 = 40.3%, P = 0.003	Fixed effect
Ankylosing spondylitis	3	3	1.18 (0.89–1.58); I^2 = 0%, P = 0.636	Fixed effect
Rheumatoid or juvenile arthritis	9	14	1.02 (0.9–1.17); I^2 = 61.7%, P = 0.572	Random effect
Systematic lupus srythematosus	6	6	1.4 (0.84–2.35); I^2 = 98.6%, P = 0.001	Random effect
Vasculitis	7	8	1.15 (0.92–1.42); I^2 = 0%, P = 0.45	Fixed effect
Other	6	15	1.04 (0.84–1.27); I^2 = 0%, P = 0.618	Fixed effect
Haematological	12	17	1.1 (0.93–1.29); I^2 = 14.8%, P = 0.28	Fixed effect
Autoimmune haemolytic anaemia	3	3	1.45 (0.79–2.63); I^2 = 0%, P = 0.86	Fixed effect
Henoch–Schonlein's purpura	4	4	1 (0.68–1.45); I^2 = 0%, P = 0.73	Fixed effect
Idiopathic thrombocytopenic purpura	9	9	1.1 (0.91–1.33); I^2 = 48.9%, P = 0.05	Fixed effect
Dermatological	7	17	1.04 (0.93–1.16); I^2 = 6.3%, P = 0.38	Fixed effect
Localized or systematic scleroderma	3	3	1.03 (0.67–1.58); I^2 = 1.5%, P = 0.362	Fixed effect
Psoriasis	4	4	0.98 (0.85–1.14); I^2 = 0%, P = 0.972	Fixed effect
Vitiligo	5	5	1.16 (0.84–1.61); I^2 = 0.8%, P = 0.4	Fixed effect
Other	5	8	1.26 (0.99–1.6); I^2 = 0%, P = 0.578	Fixed effect
Other	13	22	0.99 (0.82–1.2); I^2 = 64.9%, P < 0.001	Random effect
Type 1 diabetes	11	12	0.81 (0.63–1.04); I^2 = 70%, P < 0.001	Random effect

3.6. Gastrointestinal ADs

Ten studies reported the risk of gastrointestinal ADs in relation to HPV vaccination, and the combined OR was 1.06 (95% CI: 0.99–1.14) (Fig. S5). Analyses related to the type of gastrointestinal ADs indicated no significantly increased risk of inflammatory bowel disease (OR = 1.05, 95% CI: 0.97, 1.14), Crohn's disease (OR = 1, 95% CI: 0.86, 1.16), ulcerative colitis (OR = 1.01, 95% CI: 0.88, 1.15), celiac disease (OR = 1.12, 95% CI: 0.85, 1.47), or autoimmune pancreatitis (OR = 0.88, 95% CI: 0.73, 1.06) (Fig. S6).

3.7. Musculoskeletal or systemic ADs

Twelve studies reported the risk of musculoskeletal or systemic ADs in relation to HPV vaccination, and the combined OR was 1.07 (95% CI: 0.98–1.17) (Fig. S7). Analyses taking into account the type of musculoskeletal or systemic ADs showed that HPV vaccination was not associated with an increased risk of ankylosing spondylitis (OR = 1.18, 95% CI: 0.89, 1.58), rheumatoid or juvenile arthritis (OR = 1.02, 95% CI: 0.9, 1.17), systematic lupus erythematosus (OR = 1.4, 95% CI: 0.84, 2.35), vasculitis (OR = 1.15, 95% CI: 0.92, 1.42), or other musculoskeletal or systemic ADs (OR = 1.04, 95% CI: 0.84, 1.27) (Fig. S8).

3.8. Haematological ADs

Eleven studies reported the risk of haematological ADs in relation to HPV vaccination, and the combined OR was 1.1 (95% CI: 0.93–1.29) (Fig. S9). With respect to the type of haematological ADs, no significantly increased risk of autoimmune haemolytic anaemia (OR = 1.45, 95% CI: 0.79, 2.63), Henoch-Schönlein purpura (OR = 1, 95% CI: 0.68, 1.45), or idiopathic thrombocytopenic purpura (OR = 1.1, 95% CI: 0.91, 1.33) was found in the subgroup analyses (Fig. S10).

3.9. Dermatological ADs

Seven studies reported the risk of dermatological ADs in relation to HPV vaccination, and the combined OR was 1.04 (95% CI: 0.93–1.16) (Fig. S11). With respect to the type of dermatological ADs, no significantly increased risk of localised or systematic scleroderma (OR = 1.03, 95% CI: 0.67, 1.58), psoriasis (OR = 0.98, 95%

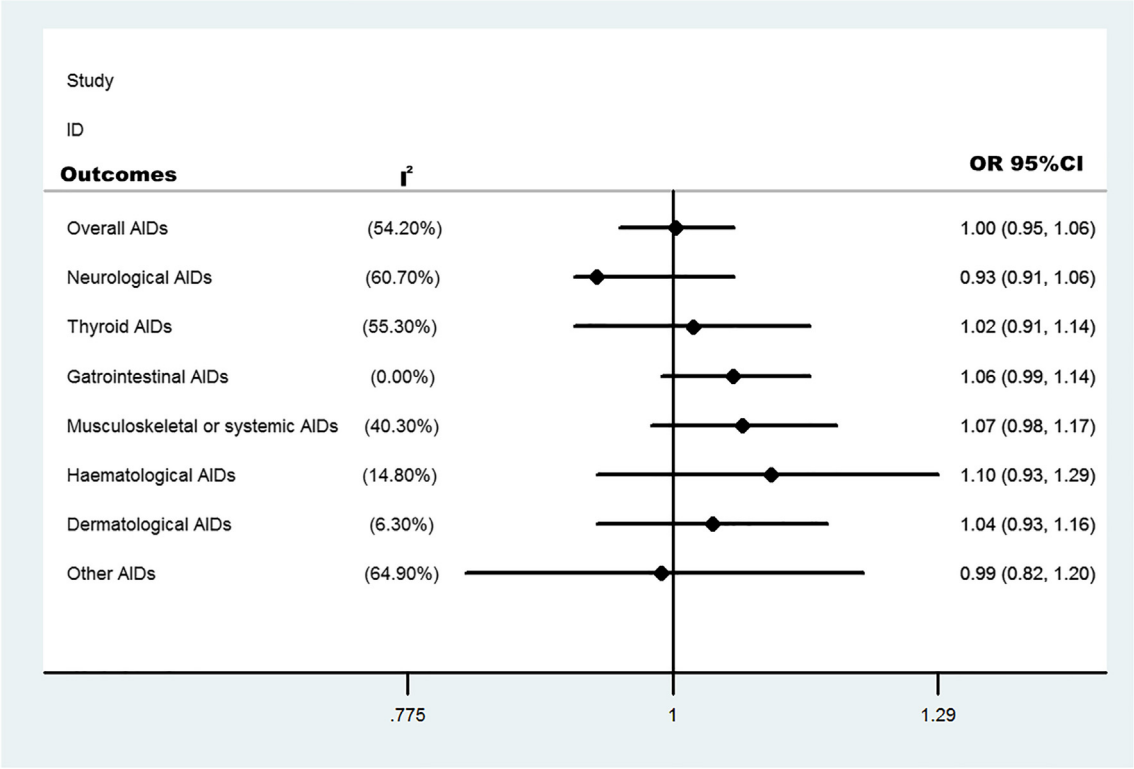

Fig. 2. Association between exposure to HPV vaccine and adverse autoimmune events (ADs).

CI: 0.85, 1.14), vitiligo (OR = 1.16, 95% CI: 0.84, 1.61), or other dermatological ADs (OR = 1.26, 95% CI: 0.99, 1.6) was found in the subgroup analyses (Fig. S12).

3.10. Other ADs

Thirteen studies reported the risk of other ADs in relation to HPV vaccination, and the combined OR was 0.99 (95% CI: 0.82–1.2) (Fig. S13). Eleven studies reported the risk of type 1 diabetes in relation to HPV vaccination, and the combined OR for type 1 diabetes was 0.81 (95% CI: 0.63–1.04) (Fig. S14).

4. Discussion

Since the regulatory approval of HPV vaccines in 2006, the risk of neurological ADs has become a growing concern due to case reports of demyelinating diseases after vaccination. However, a recent meta-analysis found no association between HPV vaccines and central demyelination [12]. It remains controversial whether HPV vaccination is associated with an increased risk of ADs other than demyelinating diseases. Therefore, there is a clear need to perform a systematic review and meta-analysis of published studies to evaluate this association comprehensively. To our knowledge, the present review is the first to assess the association between HPV vaccination and all ADs, and the findings will help us gain a better understanding of the impact of HPV vaccination on AD risk.

In this meta-analysis of 20 studies, no evidence for a link between HPV vaccination and the subsequent risk of ADs was found, even among participants with pre-existing ADs. Subgroup analyses focusing on specific types of ADs were similarly negative, suggesting that current HPV immunisation practices should continue.

The only increased risk of individual ADs among the HPV vaccine recipients was Hashimoto's thyroiditis. Hashimoto's thyroiditis is an autoimmune disease that is characterised by gradual destruction of the thyroid gland, and which frequently occurs in young female adults [41]. It is often underdiagnosed due to the lack of specific symptoms in the early stages of the disease [42]. Two studies, Chao et al.[20] and Hviid et al.[18], enrolled adult women rather than adolescent girls, as the symptoms of Hashimoto's thyroiditis may be more apparent in this age group. The vaccination visit triggers a gross examination that later results in a diagnosis; hence, a detection bias is a possible explanation for the increased pooled OR for Hashimoto's thyroiditis. Additionally, the negative association between hypothyroidism and HPV vaccination is inconsistent with the finding regarding Hashimoto's thyroiditis, which is a frequent cause of hypothyroidism. No apparent relationship was observed when we combined both outcomes in a sensitivity analysis. Therefore, our results related to the risk of Hashimoto's thyroiditis may be a random finding and should be interpreted with caution.

Another important issue is HPV vaccination among populations with autoimmune diseases. In the last 10 years, immunomodulatory and anti-tumour necrosis factor medications have been effective for inducing and maintaining remission in autoimmune patients [43,44]. These drugs make patients more susceptible to infection than healthy subjects, most of which are preventable by vaccinations [45]. Previous studies reported an increased prevalence of latent HPV infection and cervical dysplasia in patients with ADs compared with controls [46,47], supporting HPV vaccination in this population. However, HPV vaccination in autoimmune patients poses some theoretical risks of triggering a disease flare and adverse events. Unexpectedly, the pooled result of three studies found a reduced risk of new-onset ADs, suggesting a protective role of HPV vaccination for participants with ADs. Our findings are consistent with those of previous studies [48–50] that reported that the HPV vaccine is well tolerated in patients with stable

systemic lupus erythematosus and does not induce an increase in lupus activity or flares. However, this result is limited by the sample size and needs further investigation

The key strength of our meta-analysis lies in its large sample size and comprehensive search, which allows for multiple analyses based on different scenarios to increase both the study's robustness and confidence in the results. Second, this paper adds clear value to the body of evidence drawn from a previous meta-analysis, which already investigated the association between HPV vaccination and demyelinating diseases [12]. Several other neurological and other ADs were evaluated in this paper, which is especially important since additional studies have been published recently. Third, although substantial heterogeneity existed across the included studies for the association between HPV vaccination and ADs risk, we ran a subgroup analysis to examine the source of this heterogeneity.

Several limitations of the meta-analysis should be considered. First, subgroup analyses based on the type of autoimmune disorder would have been underpowered if intending to demonstrate a potential risk after HPV vaccination, the main reasons being limited included studies and the rarity of the individual outcomes of interest. Additional well-designed studies with larger samples are required to examine the association between HPV vaccination and individual autoimmune disorder risk. Second, only one study reported estimates in male recipients, and it failed to observe an association between HPV vaccination and the subsequent risk of ADs. Our findings are based on data from female recipients and thus require confirmation that the safety profile is not restricted to girls and women. Third, the definition of the vaccination exposure window was inconsistent across the included studies. Fourth, all studies included in the meta-analysis were conducted in Europe and North America; no studies were from Asian or African countries. Therefore, the findings of this meta-analysis cannot be generalised to Asian or African populations; additional observational studies from Asian or African countries are needed to provide epidemiological evidence for the influence of vaccinations on the risk of ADs in Asians or Africans.

In conclusion, the results of this meta-analysis failed to demonstrate a role for HPV vaccination in the development of ADs. The association between HPV vaccination and the risk of Hashimoto's thyroiditis should be analysed cautiously and will require further investigation. Also, there is a clear need to perform additional and larger observational studies to assess the association of HPV vaccination with ADs among male recipients.

Declaration of interest statement

The authors declare no conflict of interest

Contribution to authorship

H.Y.J. and B.R. conceived the study and revised the manuscript critically for important intellectual content. H.Y.J. and Y.D.S. made substantial contributions to its design, acquisition, analysis and interpretation of data. X.Z., L.Y.P., Y.R.X., C.M.J. and M.D. participated in the design, acquisition, analysis and interpretation of data. All authors read and approved the final manuscript.

Details of ethical approval

No ethical approval was required for this review as all data were already published in peer-reviewed journals.

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Appendix A. Supplementary material

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