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## Original Contribution

# Hospital Records of Pain, Fatigue, or Circulatory Symptoms in Girls Exposed to Human Papillomavirus Vaccination: Cohort, Self-Controlled Case Series, and Population Time Trend Studies

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Human papillomavirus (HPV) vaccination has been associated with subsequent diffuse symptoms in girls, reducing public confidence in the vaccine. We examined whether girls have nonspecific outcomes of HPV vaccination, using triangulation from cohort, self-controlled case series (SCCS), and population time trend analyses carried out in Denmark between 2000 and 2014. The study population consisted of 314,017 HPV-vaccinated girls and 314,017 age-matched HPV-unvaccinated girls (cohort analyses); 11,817 girls with hospital records (SCCS analyses); and 1,465,049 girls and boys (population time trend analyses). The main outcome measures were hospital records of pain, fatigue, or circulatory symptoms. The cohort study revealed no increased risk among HPV vaccine-exposed girls, with incidence rate ratios close to 1.0 for abdominal pain, nonspecific pain, headache, hypotension/syncope, tachycardia (including postural orthostatic tachycardia syndrome), and malaise/fatigue (including chronic fatigue syndrome). In the SCCS analyses, we observed no association between HPV vaccination and subsequent symptoms. In time trend analyses, we observed a steady increase in these hospital records in both girls and (HPV-unvaccinated) boys, with no relationship to the 2009 introduction of HPV vaccine to Denmark's vaccination program. This study, which had nationwide coverage, showed no evidence of a causal link between HPV vaccination and diffuse autonomic symptoms leading to hospital contact.

epidemiologic research design; papillomavirus; vaccination; vaccines

Abbreviations:CFS, chronic fatigue syndrome; CI, confidence interval; GP, general practitioner; HPV, human papillomavirus; IRR, incidence rate ratio; POTS, postural orthostatic tachycardia syndrome; SCCS, self-controlled case series.

Human papillomavirus (HPV) vaccination has been shown to reduce oncogenic cervical infections with vaccine-type HPV, and it thereby protects against cervical intraepithelial neoplasia and cervical cancer (1, 2). After inclusion of HPV vaccine in childhood vaccination programs in the late 2000s, safety concerns emerged in some countries, such as Denmark and Japan (3, 4). These concerns have reduced public confidence in the vaccine, resulting in substantially decreased HPV vaccine uptake in Denmark since 2015 (5). Adverse event reports and clinical case series have found several different symptoms among girls after HPV vaccination (6–9). These symptoms include pain, severe fatigue, and circulatory symptoms, which may stem from dysfunction in the autonomic nervous system (6–9).

The authors of several systematic literature reviews (10–12) and register-based studies of various analytical designs (13–15) have concluded that available data do not support a causal association between HPV vaccines and complex regional pain syndrome, autonomic dysfunction, postural orthostatic tachycardia syndrome (POTS), or chronic fatigue syndrome (CFS). However, the reviews have been criticized for omitting unpublished safety data from trials (16), leaving the HPV vaccine safety issue open for debate. Moreover, most existing observational studies have been based on inpatient hospitalizations providing specific well-defined discharge diagnoses (13–15, 17, 18). In routine clinical practice, it is common for many girls with nonspecific symptoms, which could be potential HPV vaccine side effects, to be seen

and treated in primary-care facilities, emergency rooms, or hospital outpatient clinics. Therefore, the full burden of these symptoms may not have been assessed in previous studies. Moreover, treating healthy young people requires very strong safety data.

We therefore examined the association between HPV vaccination and the risk of a range of health outcomes recorded in hospital records among girls in Denmark, using 3 different analytical approaches: cohort studies, self-controlled case series (SCCS), and population time trend studies. Since each approach may be subject to different sources of bias, taken together they provide stronger insight into the possibility of a causal relationship between HPV vaccine and the examined outcomes (19).

## METHODS

### Setting and data sources

We conducted this study in Denmark, whose cumulative population was 6,981,850 persons during 2000–2014 (20). We linked existing nationwide population-based health-care databases, including data on all HPV vaccinations and primary-care contacts, all somatic and psychiatric hospital contacts and diagnoses, and all drug prescriptions, for the entire Danish population. Accurate linkage of all registries at the individual level was possible using the unique Central Person Register number assigned to each Danish citizen at birth and to residents upon immigration (21).

We included the following 6 databases: the Danish Civil Registration System, which includes information on residence, migration, parental links, and the vital status of all Danish residents (21); the Danish National Health Service Register, which includes data on primary-care services, including general practitioner (GP) contacts, vaccinations, and psychologist or psychiatrist visits; the Danish National Patient Registry, which includes data on medical diagnoses and treatments received from all Danish nonpsychiatric hospitals (22); the Psychiatric Central Research Register, which includes data on diagnoses and treatments received in hospital psychiatric departments (23); the Danish National Prescription Registry, which includes data on all medications and vaccines bought at pharmacies in Denmark (24); and socioeconomic registries maintained by Statistics Denmark, including data on family socioeconomic variables.

### Study designs

The 3 different analytical approaches we implemented included a cohort study, an SCCS analysis, and a population time trend study (see Web Figure 1, available at https://academic.oup.com/aje).

*Cohort study: HPV-vaccinated and -unvaccinated girls.* The Danish childhood vaccination program offers HPV vaccine to girls aged 12–17 years. The first HPV vaccine was licensed for use in Denmark in 2006, and HPV vaccination has been fully implemented in the national vaccination program since 2008/2009 (18). The quadrivalent HPV vaccine was used in the program until February 2016. For the cohort study, we first identified all girls residing in Denmark who had received at least 1 dose of HPV vaccine recorded in the National Health Service Register or the National Prescription Registry between January 1, 2008, and December 31, 2014 (Web Figure 1). This study period kept our results free from any influence of the changes in HPV uptake seen in Denmark from 2015 onwards, following media reports of potential adverse events (5). Since girls are occasionally vaccinated shortly before turning 12 years of age (5), we included all girls who were between 11 and 17 years of age on their first HPV vaccination date (the index date). The vaccinated girls were then grouped into 84 monthly cohorts, according to the month and year (e.g., January 2008) of their first HPV vaccination.

HPV-unvaccinated comparison girls were selected in the following manner. For each calendar year and month (e.g., January 2008), we identified all girls in Denmark who were aged 11–17 years during that month and then allocated them to a random index date in the month of selection. Comparison girls had to be Danish residents and be alive and HPV-unvaccinated up to the index date. To ensure that they were known to the primary health-care system, both HPV-vaccinated girls and HPV-unvaccinated girls had to have at least 1 previous record in the National Health Service Register during the previous 5 years (this applied to 99.0% of vaccinated girls and 97.7% of unvaccinated girls). In each month, we then matched vaccinated girls to unvaccinated girls (1:1) by year of birth, thereby creating monthly matched cohorts. This procedure was repeated for each month during the 2008–2014 study period. Unvaccinated girls were sampled with replacement; that is, a girl could contribute risk time as an unvaccinated comparator for several HPV-vaccinated girls at different ages and index dates. Exposure to the HPV vaccine was a time-varying variable; thus, girls could contribute person-time to the study first as unvaccinated participants and later as vaccinated participants (but after they were vaccinated, girls could not reenter the unvaccinated cohort).

*Outcomes and confounders.* The main study outcomes were the following types of hospital records, predefined in the protocol: a first hospital contact with abdominal pain, nonspecific pain, headache, malaise or fatigue (including CFS), tachycardia (including POTS), and hypotension or syncope. We also identified several negative control outcomes not generally believed to be related to HPV vaccination. These included hospital records of trauma, diabetes mellitus, cancer, pneumonia, asthma, and appendicitis, as well as all-cause death (codes provided in Web Table 1).

Potential confounders were assessed through both hospital and primary-care contacts and prescription data up to the index date. They included previously treated somatic and mental disorders, primary-care contact patterns and services, parental socioeconomic factors, and ethnicity.

*Cohort study: statistical analysis.* We followed the vaccinated and unvaccinated girls after the vaccination/index date and examined how many had a hospital record of each separate study outcome. We predefined the period at risk as 1 year (360 days) following HPV vaccination, to allow

for insidious onset and possible diagnostic delay for the symptoms under study, while defining a follow-up period where the symptoms could still be plausibly related to vaccination (17). Girls with a study outcome before their index date were excluded from the primary cohort analysis. In a secondary cohort analysis, we ignored the presence of prior outcome events. In our primary analysis, we compared 1-year rates of outcomes, not taking into account eventual later vaccine exposure among unvaccinated girls. In a secondary analysis, we compared 1-year outcome rates, with censoring of unvaccinated girls at the date of later vaccination if they were HPV-vaccinated during the 1-year follow-up period. We calculated incidence rate ratios (IRRs) by comparing 1-year outcome rates in vaccinated and unvaccinated girls, using Cox regression analysis to adjust for age, calendar year of study entry, baseline comorbid conditions (history of hospital contact for asthma, diabetes, infection, or mental disorders), previous community psychologist or psychiatrist visits, previous psychometric testing or oral talk therapy with a GP, prior frequency of GP contacts, and ethnicity, as well as parental education, employment, income, and marital status.

*SCCS analysis.* SCCS analysis is a case-only method in which only persons who have experienced an outcome are included (25). Individuals serve as their own controls, and all time-stable confounding is eliminated by design (26). We used the SCCS method to examine whether outcomes happened more frequently within the exposure risk period (i.e., 1 year after HPV vaccination) than during a baseline reference period. Web Figure 1 depicts the overall SCCS study design. We initially identified all girls in Denmark who had both their 11th birthday and their 18th birthday between 2000 and 2014—that is, girls born during 1989–1996 ($n$ = 272,004). We then included all girls who had their first-ever study outcome between the ages of 11 and 17 years ($n$ = 11,817). Using a conditional Poisson model, we estimated the IRR for hospital record outcomes and several negative control outcomes during the HPV vaccine exposure risk period as compared with the baseline reference period. To control for increasing age in the study period, we included age in the model in addition to calendar year.

Because it was unlikely for a girl to have been vaccinated against HPV shortly after being diagnosed with one of the health outcomes under study (e.g., syncope), we excluded a preexposure washout period of 21 days before HPV vaccination from the baseline period. All time within the study period that was not included in either the preexposure period or the exposure period was considered baseline period (reference) time. Girls with a health outcome who had not been HPV-vaccinated could also contribute unexposed reference time, to increase the precision of the age and calendar year estimates (26).

*Population time trend analysis.* The rationale of the time trend analysis was to ascertain any increase or decrease in records of pain, fatigue, or circulatory symptoms in girls versus boys after introduction of HPV vaccine into the vaccination program in 2009, knowing that boys remained largely HPV-unvaccinated during the study period. We used hospital contact data on the study outcomes discussed above over a longer time period (i.e., between 2000 and 2014) to examine overall time trends in nationwide incidence per 100,000 person-years among all girls and boys who were 11–17 years of age at any time during 2000–2014 ($n$ = 1,465,049) (Web Figure 1). We plotted annual HPV vaccination coverage (percent) among Danish girls and boys as a point of comparison.

The study protocol was approved by the Danish Data Protection Agency. According to Danish legislation, approval from an ethics committee is not required for registry-based studies.

## RESULTS

### Cohort analysis

A total of 314,017 girls who were HPV-vaccinated at ages 11–17 years between 2008 and 2014 were eligible for inclusion in the vaccinated cohort. From all 442,229 girls aged 11–17 years in the source population, we sampled 177,724 unique girls who served as 314,017 matched unvaccinated comparators. These girls had not received an HPV vaccine on the index date of the HPV-vaccinated girls (56% of the 177,724 girls acted as an unvaccinated comparator to 1 vaccinated girl only, 25% to 2 vaccinated girls, and 19% to 3 or more vaccinated girls).

A slight "healthy vaccinee effect" was observed; that is, girls who were vaccinated against HPV had a slightly lower prevalence of prior hospital-diagnosed comorbidity than unvaccinated girls, but they also tended to have more prior GP contacts (Table 1). Parents of vaccinated girls and unvaccinated girls had similar educational levels (14.1% vs. 13.7% with higher education), but more were employed (both parents working: 72.0% vs. 65.4%), and parental income was slightly higher (53.1% vs. 46.8% earned more than 650,000 Danish kroner (>€87,090) per year). It was also more common for HPV-vaccinated girls to have married parents (64.0% vs. 59.1%) and to be nonimmigrants (90.8% vs. 88.4%) (Table 1).

The hospital contact rate for abdominal pain was 7.8 per 1,000 person-years during the first year following HPV vaccination versus 8.3 per 1,000 person-years among unvaccinated girls (Table 2). After adjustment, the corresponding IRR for abdominal pain was 0.91 (95% confidence interval (CI): 0.86, 0.97) when comparing vaccinated girls with unvaccinated girls. Adjusted IRRs for vaccine-exposed versus unexposed girls were close to 1 for other symptoms: 1.09 (95% CI: 0.96, 1.22) for headache, 0.95 (95% CI: 0.79, 1.14) for nonspecific pain, 0.96 (95% CI: 0.88, 1.06) for hypotension/syncope, 1.14 (95% CI: 0.87, 1.50) for tachycardia (including an IRR of 0.54 (95% CI: 0.19, 1.53) for the POTS subdiagnosis), and 0.90 (95% CI: 0.68, 1.17) for malaise/fatigue (including an IRR of 0.12 (95% CI: 0.02, 0.99) for the CFS subdiagnosis). Most of the adjusted IRRs were close to the crude estimates. The risk of death was markedly lower in vaccinated girls than in unvaccinated girls (IRR = 0.52, 95% CI: 0.27, 0.97).

IRRs for hospital records created during emergency room visits, hospital outpatient clinic visits, and inpatient admis-

**Table 1.** Characteristics of Girls Aged 11–17 Years and Their Parents by Human Papillomavirus Vaccination Exposure (Matched Cohort Study), Denmark, 2008–2014

| Characteristic | HPV-Unvaccinated Girls (*n* = 314,017) | | HPV-Vaccinated Girls (*n* = 314,017) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Girl's medical history prior to index date | | | | |
| Asthma | 17,756 | 5.7 | 7,072 | 5.4 |
| Infection | 25,764 | 8.2 | 23,686 | 7.5 |
| Diabetes mellitus | 1,289 | 0.4 | 1,057 | 0.3 |
| Mental disorder | 10,036 | 3.2 | 7,327 | 2.3 |
| Previous psychologist or psychiatrist visit | 6,489 | 2.1 | 5,676 | 1.8 |
| Previous psychometric test or talk therapy with GP | 9,866 | 3.1 | 8,728 | 2.8 |
| >50 previous GP contacts | 73,123 | 23.3 | 81,009 | 25.8 |
| Girl's parents | | | | |
| Higher education (university) | 42,960 | 13.7 | 44,110 | 14.1 |
| Both employed | 205,433 | 65.4 | 226,108 | 72.0 |
| Annual income above median (>€87,090) | 146,836 | 46.8 | 166,588 | 53.1 |
| Married | 185,523 | 59.1 | 201,026 | 64.0 |
| Danish ethnicity (nonimmigrants) | 277,704 | 88.4 | 285,238 | 90.8 |

Abbreviations: GP, general practitioner; HPV, human papillomavirus.

sions are shown separately in Web Table 2. An analysis stratified by calendar year of cohort entry yielded results similar to those of the main analysis (data not shown). Adjusted IRRs for the negative control outcomes were mostly close to 1.0 (Table 2). Cohort analyses with censoring at vaccination among the unvaccinated comparison girls yielded similar results, except that hospital contacts involving tachycardia and diabetes tended to be increased (Web Table 3). Cohort analyses ignoring prior outcome events in vaccinated and unvaccinated girls yielded results very similar to those of the main analysis (Web Table 4).

### SCCS analysis

Of 272,004 girls who were aged 11–17 years during the period 2000–2014 (Figure 1), 54.7% received HPV vaccine. The numbers of cases with the different outcomes under study are shown in Web Figure 1 and Table 3. There was no substantial association between HPV vaccination and headache (among 2,997 girls with a record of headache, IRR = 1.14, 95% CI: 0.99, 1.32), pain (among 1,370 girls with a record of pain, IRR = 0.85, 95% CI: 0.68, 1.06), hypotension/syncope (among 5,788 girls with such records, IRR = 1.02, 95% CI 0.92, 1.14), tachycardia (among 808 girls with such records, IRR = 0.93, 95% CI: 0.70, 1.24), malaise/fatigue (among 830 girls with such records, IRR = 1.09, 95% CI: 0.83, 1.45), or CFS (among 24 girls with this diagnosis, IRR = 0.82, 95% CI: 0.16, 4.16) (Table 3, Web Figure 2). Because of lack of convergence, it was not possible to study associations with abdominal pain or POTS.

### Population time trend analysis

In population time trend analyses, between 2000 and 2014, we observed a steady increase in Danish girls and boys with a hospital record related to pain, malaise/fatigue, hypotension/syncope, and tachycardia (Figure 1). No clear change occurred after the introduction of HPV vaccine into the vaccination program. While HPV vaccination coverage rose sharply among girls after 2008, boys remained largely unvaccinated for HPV throughout the study period (Figure 1).

## DISCUSSION

We found no increased rates of hospital records related to pain, fatigue, or circulatory symptoms in girls exposed to HPV vaccine versus unexposed girls. Similarly, when girls with such records served as their own controls, no association was observed for HPV vaccination. Furthermore, at the Danish population level, rates of these hospital records steadily increased over time in both girls and boys—unrelated to the timing of introduction of HPV vaccination.

### Study strengths and limitations

Major strengths of our study are its population-based design, participants' free access to health care, and complete follow-up, all of which limited selection bias. We used routinely collected, individual-level health-care records to conduct this study. This minimizes concern over recall and ascertainment bias, since both vaccination data and data on

**Table 2.** Incidence Rate Ratios for Specific Health Outcomes in Hospital Records Among Girls Aged 11–17 Years by Human Papillomavirus Vaccination Exposure (Matched Cohort Study), Denmark, 2008–2014

| Health Outcome | HPV-Unvaccinated Girls (*n* = 314,017) | | | HPV-Vaccinated Girls (*n* = 314,017) | | | Crude IRR | 95% CI | Adjusted[a] IRR | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of Outcomes | PY of Follow-up | IR per 1,000 PY | No. of Outcomes | PY of Follow-up | IR per 1,000 PY | | | | |
| Main outcomes | | | | | | | | | | |
| Abdominal pain | 2,465 | 295,414 | 8.34 | 2,303 | 296,133 | 7.78 | 0.93 | 0.88, 0.99 | 0.91 | 0.86, 0.97 |
| Headache | 583 | 310,593 | 1.88 | 618 | 310,708 | 1.99 | 1.06 | 0.95, 1.19 | 1.09 | 0.96, 1.22 |
| Nonspecific pain | 269 | 312,736 | 0.86 | 265 | 312,825 | 0.85 | 0.98 | 0.83, 1.17 | 0.95 | 0.79, 1.14 |
| Hypotension/syncope | 938 | 309,937 | 3.03 | 908 | 310,128 | 2.93 | 0.97 | 0.88, 1.06 | 0.96 | 0.88, 1.06 |
| Tachycardia | 109 | 313,243 | 0.35 | 122 | 313,296 | 0.39 | 1.12 | 0.86, 1.45 | 1.14 | 0.87, 1.50 |
| POTS | 10 | 313,871 | 0.03 | 6 | 313,880 | 0.02 | 0.60 | 0.22, 1.65 | 0.54 | 0.19, 1.53 |
| Malaise/fatigue | 124 | 313,514 | 0.40 | 112 | 313,560 | 0.36 | 0.90 | 0.70, 1.17 | 0.90 | 0.68, 1.17 |
| CFS | 9 | 313,859 | 0.03 | —[b] | 313,879 | — | 0.11 | 0.01, 0.88 | 0.12 | 0.02, 0.99 |
| Death | 32 | 313,885 | 0.10 | 16 | 313,894 | 0.05 | 0.50 | 0.27, 0.91 | 0.52 | 0.27, 0.97 |
| Negative control outcomes | | | | | | | | | | |
| Trauma | 8,966 | 102,383 | 87.57 | 8,825 | 101,801 | 86.69 | 0.99 | 0.96, 1.02 | 0.99 | 0.96, 1.02 |
| Diabetes mellitus | 139 | 312,538 | 0.44 | 141 | 312,761 | 0.45 | 1.01 | 0.80, 1.28 | 1.13 | 0.88, 1.45 |
| Cancer | 50 | 313,308 | 0.16 | 52 | 313,413 | 0.17 | 1.04 | 0.71, 1.53 | 0.96 | 0.65, 1.43 |
| Pneumonia | 199 | 300,070 | 0.66 | 133 | 301,392 | 0.44 | 0.67 | 0.53, 0.83 | 0.67 | 0.53, 0.84 |
| Asthma | 601 | 295,791 | 2.03 | 555 | 296,506 | 1.87 | 0.92 | 0.82, 1.03 | 0.95 | 0.84, 1.07 |
| Appendicitis | 656 | 309,028 | 2.12 | 618 | 308,960 | 2.00 | 0.94 | 0.84, 1.05 | 0.90 | 0.81, 1.01 |

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; HPV, human papillomavirus; IR, incidence rate; IRR, incidence rate ratio; POTS, postural orthostatic tachycardia syndrome; PY, person-years.

[a] Adjusted via Cox regression for age (years; continuous), calendar year of cohort entry (2008–2014), histories of hospital-diagnosed asthma (yes/no), diabetes (yes/no), infections (yes/no), and mental disorders (yes/no), number of general practitioner contacts within the past 5 years (continuous), previous psychometric tests or talk therapy with a general practitioner (yes/no), a previous psychologist or psychiatrist visit in primary care (yes/no), parental education (primary, secondary, or higher), parental employment status (neither parent, 1 parent, or both), parental annual income in Danish kroner (≤kr.450,000, kr.450,001–kr.650,000, kr.650,001–kr.850,000, or >kr.850,000), parental marital status (married, other), and parental ethnicity (non-Danish (immigrants), Danish).

[b] The number of events was too low to be displayed according to Danish data protection regulations.

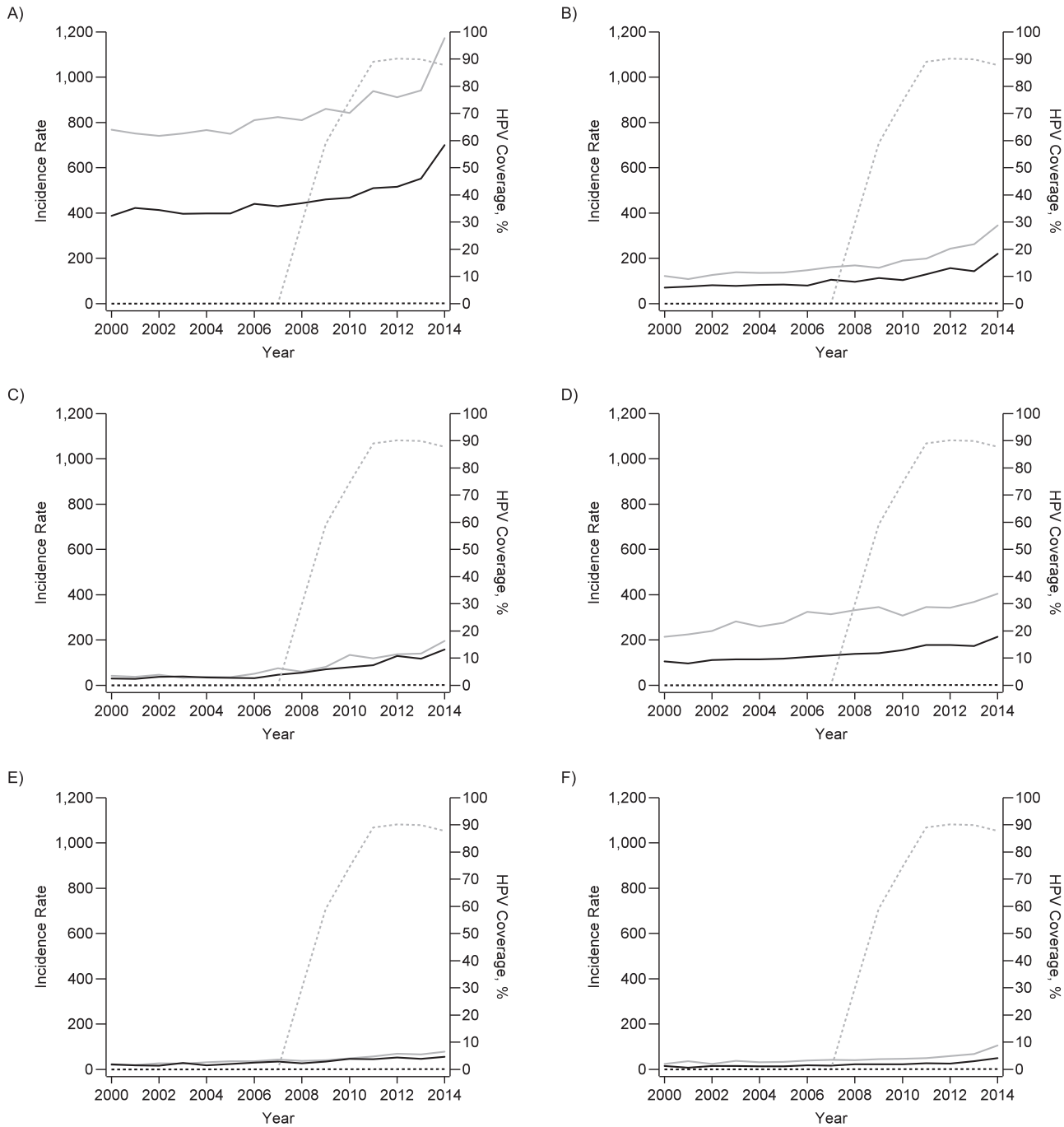


**Figure 1.** Incidence of specific health outcomes in hospital records among girls and boys aged 11–17 years (population time trend study), Denmark, 2000–2014. The graph shows time trends in nationwide incidence of the following outcomes per 100,000 person-years of hospital records among girls (gray line) and boys (black line): abdominal pain (A), headache (B), nonspecific pain (C), hypotension/syncope (D), tachycardia (E), and malaise/fatigue (F). The gray dashed line and the black dashed line show annual human papillomavirus (HPV) vaccination coverage in girls and boys, respectively.

subsequent hospital contacts were collected prospectively (18). We thus avoided any effect on the diagnostic process sparked by the research question. In the cohort analysis, we were able to adjust for a wide range of confounding factors. The source population consisted of the entire Danish population, with rates of hospital records based on true general population rates in young people, and our results are likely to be generalizable to other time periods and populations.

**Table 3.** Incidence Rate Ratios for Specific Health Outcomes in Hospital Records Among Girls Aged 11–17 Years During the Human Papillomavirus Vaccine Exposure Risk Period as Compared With the Baseline Reference Period (Self-Controlled Case Series Analysis), Denmark, 2000–2014

| Health Outcome | No. of Outcomes | No. of Girls Exposed to HPV Vaccine | IRR | 95% CI |
|---|---|---|---|---|
| Main outcomes | | | | |
| Abdominal pain | —[a] | — | — | |
| Headache | 2,997 | 1,796 | 1.14 | 0.99, 1.32 |
| Nonspecific pain | 1,370 | 859 | 0.85 | 0.68, 1.06 |
| Hypotension/syncope | 5,788 | 3,188 | 1.02 | 0.92, 1.14 |
| Tachycardia | 808 | 503 | 0.93 | 0.70, 1.24 |
| POTS | — | — | — | |
| Malaise/fatigue | 830 | 488 | 1.09 | 0.83, 1.45 |
| CFS | 24 | 13 | 0.82 | 0.16, 4.16 |
| Death | — | — | — | |
| Negative control outcomes | | | | |
| Trauma | — | — | — | |
| Diabetes mellitus | 583 | 343 | 1.10 | 0.78, 1.53 |
| Cancer | 309 | 180 | 1.17 | 0.76, 1.78 |
| Pneumonia | 1,047 | 561 | 0.66 | 0.49, 0.88 |
| Asthma | 3,672 | 2,060 | 1.02 | 0.89, 1.17 |
| Appendicitis | 4,128 | 2,279 | 0.90 | 0.78, 1.03 |

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; HPV, human papillomavirus; IRR, incidence rate ratio; POTS, postural orthostatic tachycardia syndrome.

[a] Because of lack of convergence, it was not possible to study the association with abdominal pain, POTS, or trauma in the self-controlled case series analysis; death cannot be examined in self-controlled case series analysis.

The findings of no association between HPV vaccine and unwarranted unspecific outcomes are strengthened by our triangulation strategy—that is, the use of different analytical methods to address the same research question (19). Because our different methods inherently had different assumptions, strengths, and weaknesses, our overall conclusion, based on multiple analytical methods, of no evidence of a causal link between HPV vaccination and diffuse autonomic symptoms provides evidence for consistency—one of the main criteria for causality.

Our study also has limitations. First, while the quality of diagnoses in the Danish National Patient Registry is generally high for major diseases (22), the specificity of diagnostic coding related to pain, malaise, fatigue, or circulatory symptoms is not known. Validation studies of these codes may also prove difficult to conduct, given the subjective nature and lack of a gold standard for many of the symptoms. If knowledge of prior exposure to HPV vaccination had led to increased probability of clinicians' coding false-positive outcomes, this would have led to overestimation of risks from HPV vaccination, which would not change our conclusions. Second, HPV vaccinations are usually associated with health-care contacts with GPs, and these contacts may have led to closer evaluation and possibly unmasking of and hospital referral for symptoms that were already prevalent at the time of vaccination. After HPV vaccination, published case reports (3) and the beginning of a public debate in Denmark questioning the safety of the HPV vaccine (5) may also have led to increased care-seeking behavior in vaccinated girls and to increased attention and diagnostic workups on the part of physicians. This would have inflated any association between HPV vaccination and symptoms, and our null results speak against the importance of such bias. The possible side-effect debate in Denmark started late in 2013, at the very end of our cohort study period, and is thus unlikely to have had a major influence on our findings. Finally, although residual confounding was a possibility in our cohort analyses, we adjusted for a wide range of potential confounders, and influence from adjustment appeared to be minor based on comparison of crude and adjusted IRRs. Moreover, the SCCS analysis implicitly controls for time-independent confounders and suggested that unmeasured confounding was minimal, confirming our cohort analysis results.

### Comparison with other studies

In accordance with our findings, in a cross-sectional study in California, Chao et al. (27) observed that HPV-vaccinated girls had a higher historical level of primary-care visits but less history of hospital-diagnosed severe conditions. This may be related to frequent interactions with primary-care providers facilitating the decision to vaccinate, whereas care

of hospitalized girls with more severe conditions may have a focus other than preventive care needs (27). Our findings of lower uptake of HPV vaccine in children of non-Danish parents, unmarried parents, and parents with a lower socioeconomic status are also in line with previous research (5).

Few previous large-scale studies have addressed the association between HPV vaccination and general hospital records while including nonspecific symptoms and signs. Skufca et al. (28) examined 240,605 HPV-vaccinated and -unvaccinated girls aged 11–15 years in Finland. Corroborating our findings, HPV vaccination was not associated with increased risk of malaise/fatigue, CFS, or POTS. Notably, diagnoses of malaise and fatigue increased steadily over calendar time among Finnish youth, not only in girls but also in (HPV-unvaccinated) boys (28), in line with our findings.

Two large studies from the United Kingdom (13) and Norway (14) specifically addressed HPV vaccination and chronic fatigue syndromes. Donegan et al. (13) conducted an ecological analysis and an SCCS analysis, both using data from the Clinical Practice Research Datalink. They found no change in the incidence of CFS/myalgic encephalomyelitis or postviral fatigue syndrome in girls aged 12–20 years after introduction of the HPV vaccine in the United Kingdom and no evidence of an increased risk of these fatigue syndromes 1 year after the first vaccination (IRR = 1.07, 95% CI: 0.57, 2.00); both results corroborate our findings. Feiring et al. (14) examined incidence rates of CFS/myalgic encephalomyelitis during 2009–2014 among 824,133 Norwegian boys and girls aged 10–17 years. HPV vaccination was not associated with CFS/myalgic encephalomyelitis in girls 2 years after vaccination (hazard ratio = 0.96, 95% CI: 0.64, 1.43). There was a steady increase in incidence rates of CFS/myalgic encephalomyelitis observed among both girls and boys, corresponding to the Finnish findings of Skufca et al. (28) and our own findings.

In a recent Dutch primary-care study, Schurink-Van't Klooster et al. (29) found no significantly elevated risk of long-term fatigue associated with HPV vaccination in 12- to 16-year-old girls, either in relation to the introduction of HPV vaccination in the Netherlands or when examined in an SCCS analysis. These findings are consistent with a recent questionnaire survey study from Japan (30) and an analysis of adverse-event reports from Italy (31).

### Implications

After a period of intense public debate on HPV vaccine safety concerns in Denmark (5) and internationally (9, 16), vaccine uptake in Denmark reportedly has increased during the last 2 years (5). Our current study adds to data that support a favorable safety profile of the HPV vaccine, by providing comprehensive analyses of a range of symptoms and conditions related to possible autonomic nervous system dysfunction.

## CONCLUSION

In this study with nationwide coverage, HPV vaccination among girls was not associated with subsequent increased risk of pain, malaise, fatigue, tachycardia, hypotension, or syncope. These findings do not cause concern about a causal link between HPV vaccination and diffuse autonomic symptoms leading to hospital contacts.

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