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# Narcolepsy and hypersomnia in Norwegian children and young adults following the influenza A(H1N1) 2009 pandemic

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ABSTRACT

*Background:* Associations between influenza infection and sleep disorders are poorly studied. We investigated if pandemic influenza infection or vaccination with Pandemrix in 2009/2010 was associated with narcolepsy or hypersomnia in children and young adults.
*Methods:* We followed the Norwegian population under age 30 from January 2008 through December 2012 by linking national health registry data. Narcolepsy diagnoses were validated using hospital records. Risks of narcolepsy or hypersomnia were estimated as adjusted hazard ratios (HRs) in Cox regression models with influenza infection and vaccination as time-dependent exposures.
*Results:* Among the 1,638,526 persons under age 30 in Norway in 2009, 3.6% received a physician diagnosis of influenza during the pandemic, while 41.9% were vaccinated against pandemic influenza. Between October 1st 2009 and December 31st 2012, 72 persons had onset of narcolepsy and 305 were diagnosed with hypersomnia. The risk of a sleep disorder was associated with infection during the first six months, adjusted HR 3.31 with 95% confidence interval [CI], 1.01–10.79 for narcolepsy and adjusted HR 3.13 (95% CI, 1.12–8.76) for hypersomnia. The risk of narcolepsy was strongly associated with vaccination during the first six months adjusted HR 17.21 (95% CI, 6.28–47.14), while the adjusted HR for hypersomnia was 1.54 (95% CI, 0.81–2.93).
*Conclusions:* The study confirms an increased HR of narcolepsy following pandemic vaccination. Slightly increased HRs of narcolepsy and hypersomnia are also seen after influenza infection. However, the role of infection should be viewed with caution due to underreporting of influenza.


## 1. Introduction

During the 2009 Influenza A (H1N1) pandemic, vaccination was recommended in many countries. After the pandemic, increasing numbers of children and young adults with complaints of excessive daytime sleepiness (EDS) [1] were observed in many countries, including Norway [2–7]. Some patients with EDS were subsequently diagnosed with Narcolepsy, and a causal link to immunisation with a specific ASO3 adjuvanted influenza A H1N1 vaccine (Pandemrix) has been suggested [2–7]. EDS is a cardinal symptom in sleep disorders of central nervous origin, including narcolepsy and idiopatic hypersomnia [1].

The etiologies of narcolepsy and idiopatic hypersomnia are unknown [8]. Two types of narcolepsy are clinically recognized [1]. Both present with EDS and pathological scores in multiple sleep latency tests (MSLT). As opposed to type 2 narcolepsy, type 1 is complicated by cataplexy and low hypocretin-1 levels in cerebrospinal fluid (CFS) [1]. Recent studies suggest that narcolepsy type 1 is an autoimmune disease in which hypocretin-producing neurons important in regulation of sleep are destroyed [8–10]. Less is known about the pathophysiological mechanisms causing narcolepsy type 2 [1].

We are not aware of any publications addressing whether pandemic influenza/Pandemrix vaccination is associated with hypersomnia. However, anecdotal reports of patients with hypersomnia who claimed compensation after Pandemrix vaccination encouraged inclusion of this outcome in the current study.

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Idiopathic hypersomnia presents with excessive sleep in absence of other symptoms. No biological markers have been identified, and the pathophysiology is unknown [11]. Diagnostic criteria are defined according to the International Classification of Sleep Disorders (ICSD) [1] as either daily, irrepressible need to sleep or daytime lapses of sleep persisting for at least 3 months. The diagnosis requires absence of cataplexy [1]. Thus the clinical features of narcolepsy type 2 and idiopathic hypersomnia are very similar [11].

In Norway, the vaccination campaign coincided with the peak of the influenza pandemic. The association between influenza infection and narcolepsy is largely unknown, and the effects of exposure to both influenza infection and vaccination have not been described. We had the opportunity to study narcolepsy and hypersomnia in children and young adults using nationwide registries including information on *both* influenza infection and vaccination.

## 2. Materials and methods

### 2.1. Study population

The study population comprised all individuals born after 1982 who were registered in the National Registry as residents and living in Norway on October 1st 2009, counting 1,638,526 individuals aged 3–29 years at end of follow-up (December 31st, 2012) [12]. The study population was followed from January 2008 through December 2012. All Norwegian citizens have a unique personal identification number, allowing linkage of individual exposure and outcome data from national registries, hospital records and other data sources. The study was approved by the Regional Committee for Medical and Health Research Ethics South East and the Norwegian Data Protection Authority. All authors vouch for the integrity of the data and accuracy of the analysis. The manufacturers of the vaccine that was analyzed had no role in the study.

### 2.2. Datasources, exposures and outcomes

#### 2.2.1. Influenza infection and vaccination

The main wave of the influenza A (H1N1) pandemic in Norway lasted from October 1st to December 31st, 2009 according to influenza surveillance data from the Norwegian Institute of Public Health based on laboratory diagnoses and clinical reports [13]. Only influenza diagnoses from this peak period were included in the analyses.

Exposure to influenza was defined either as a primary care physician contact leading to a clinical diagnosis of influenza according to the International Classification of Primary Care, Second Edition (ICPC-2), code R80 [14], or as laboratory confirmed influenza A (H1N1) pdm09 infection. Information on primary care influenza diagnoses were provided by the Norwegian Directorate of Health (reimbursement data) [15]. The Norwegian Directorate of Health reimburses consultations in emergency outpatient clinics and general practice. We used information on dates of physician consultations for individuals receiving an influenza diagnoses in the ICPC-2 code system.

Data on laboratory-confirmed cases of influenza were provided by the Norwegian Surveillance System for Communicable Diseases [13]. This registry is a nationwide system for surveillance of infectious diseases based on individual records.

Influenza vaccination was offered free of charge to the entire Norwegian population from October 19th, 2009. Individuals with medical risk factors for severe influenza illness and complications were prioritized for vaccination early in the campaign. Nearly all vaccinations (97%) were administered by December 31st, 2009. Registration of influenza vaccinations was mandatory, and the data are considered almost complete [16]. Dates of influenza vaccination for all individuals were extracted from the Norwegian Immunisation Registry [16].

#### 2.2.2. Narcolepsy

Information on narcolepsy diagnoses, code G47.4 in the International Classification of Diseases, version 10 (ICD-10) from specialist health care services during 2008–2012 was obtained from the Norwegian Patient Registry (NPR) [17]. The NPR is an administrative database to which all Norwegian hospitals and outpatient clinics report to receive governmental reimbursement. Children with narcolepsy were identified by the first registration of narcolepsy (ICD-10 code G47.4) in the NPR. In- and out-patient hospital records for patients registered with ICD-10 code G47.4 were reviewed by two physicians (authors SEH and LT) for case ascertainment and extraction of relevant clinical data. Narcolepsy was classified in three levels according to the Brighton Collaboration definition (Supplementary Table 1) [18]. Level 1 includes cataplexy and hypocretin-1 deficiency corresponding to narcolepsy type1 [1]. For patients with a persistent, clinical diagnosis of narcolepsy recorded in the hospital record but missing information on diagnostic criteria, a fourth level of diagnostic certainty was defined (Supplementary Table 1). These patients were also defined as cases. Information on month and year of symptom onset was extracted from hospital records.

#### 2.2.3. Hypersomnia

Information on hypersomnia (ICD-10 code G47.1) was obtained from the NPR [17]. The date of the first registered diagnosis was used in the main analyses since review of hospital records for patients registered with ICD-10 code G47.1 was not feasible due to large number of records thus timing of symptom onset could not be obtained.

### 2.3. Statistical analysis

We applied a Cox proportional-hazards regression to estimate crude and adjusted hazard ratios (HRs) of narcolepsy and hypersomnia, with months from October 1st 2009 as the time metric and vaccination and influenza infection as time varying exposures. Subjects were considered exposed to infection from the month of first influenza diagnosis *or* first positive laboratory test. Hazard ratios (HRs) after influenza infection were calculated for three exposure periods: 6 months, 12 months, and until the end of follow-up (December 31st, 2012). Exposure to the vaccine was defined from the month of vaccination and HRs calculated for the same exposure periods.

For adjusted estimates, we used a stratified Cox proportional-hazards regression model with sex and age (categorized into the groups 3–9 years, 10–19 years, and 20–29 years) as stratification variables and mutual adjustment for influenza and vaccination status. Follow-up ended at the month of emigration, death, first symptom of narcolepsy, first diagnosis of hypersomnia or end of follow-up, whichever occurred first. Analyses were performed with the use of Stata 14 software, (Stata Corp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

## 3. Results

The weekly numbers of positive influenza laboratory tests, and vaccinations according to the pandemic peak are illustrated in Fig. 1. Primary care contacts for influenza like illness, ILI, showed a similar timely distribution as the weekly number of laboratory confirmed influenza cases (results not shown in the figure). Children were not considered a prioritized group for pandemic vacci-

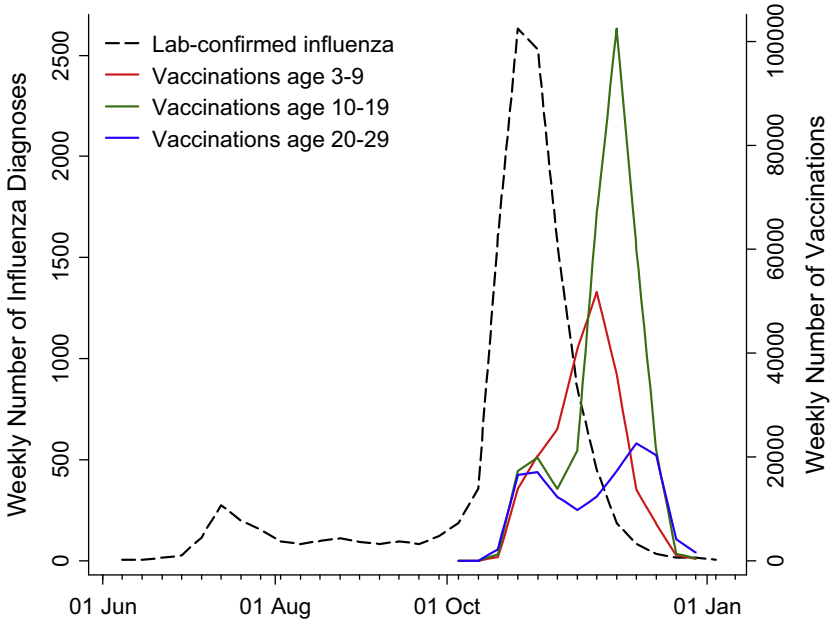


**Fig. 1.** Temporal distributions of vaccinations by age groups, and timing of the pandemic peak shown by the weekly number of positive influenza A H1N1pdm09 virus laboratory tests in the Norwegian population (all ages).

nation, and were mainly vaccinated after the main pandemic peak (Fig. 1).

A clinical or laboratory-confirmed diagnosis of influenza was recorded in 59,107 persons (3.6%). A total of 687,982 persons (41.9%) were vaccinated (Table 1). Influenza showed little variation across sex and age groups. However, the clinical attack rate of influenza is likely to be much higher than recorded and it is probable that subclinical and mild cases have been underreported since they have not received health care. Vaccination coverage was slightly higher in females and lower in the older age groups.

### 3.1. Narcolepsy

Narcolepsy was reported in the NPR for 216 persons under the age of 30. Hospital records were available for review for 214 persons, and the narcolepsy diagnosis was confirmed according to the Brighton Collaboration definition or a clinical diagnosis of narcolepsy in 130 patients (60%), among whom 71 were female. Sixty-five (50%) of the 130 patients fulfilled the criterions corresponding to narcolepsy type 1. Sixteen patients had a persistent clinical diagnosis without fulfillment of diagnostic criteria (Supplementary Table 1). More information on narcolepsy characteristics, hypocretin-1 levels and cataplexy, is supplied in the Supplementary appendix.

**Table 1**
Vaccination coverage and influenza illness by sex and age[a] during the 2009 influenza pandemic, Norway.

| Characteristic | No. of subjects | Diagnosed with Influenza *percent* | Vaccinated *percent* |
|---|---|---|---|
| Total | 1,638,526 | 3.6 | 41.9 |
| *Sex* | | | |
| Male | 839,022 | 3.4 | 40.1 |
| Female | 799,504 | 3.7 | 43.9 |
| *Age* | | | |
| 3–9 yr | 404,537 | 3.7 | 52.8 |
| 10–19 yr | 619,542 | 3.6 | 53.2 |
| 20–29 yr | 614,447 | 3.5 | 23.4 |

[a] Age by end of follow up (December 2012).

In 48 patients, symptoms of narcolepsy had started prior to 2008. Eighty-two children and young adults had new onset narcolepsy during the study period from 2008 to 2012. The number with new onset narcolepsy peaked in 2010 and subsequently declined (Fig. 2, panel A). In 72 patients, narcolepsy onset was dated after October 1st 2009.

### 3.2. Influenza and risk of narcolepsy

The number of children seeking medical care for influenza during the pandemic was low, and only four patients had registered onset of narcolepsy after a clinical diagnosis of influenza. Among these, three were also vaccinated - two of them *after* they had influenza. The HR for narcolepsy after influenza infection was two to threefold increased (Table 2). Within the 6 months exposure period, the adjusted HR was 3.31 (95% confidence interval [CI], 1.01–10.79). In a sensitivity analysis using date of narcolepsy diagnosis in the NPR instead of symptom onset as extracted from the hospital records, the aHR for narcolepsy within the entire follow-up period was 1.67 (95% CI, 0.68–4.12), quite similar to the aHR using symptom onset, 1.96 (95% CI, 0.71–5.37). The time between infection and onset of narcolepsy symptoms was between 5 and 14 months.

### 3.3. Vaccination and risk of narcolepsy

The HR for narcolepsy was increased in children and young adults after pandemic vaccination (Table 2), with highest estimates within short exposure periods (adjusted HRs, 6 months: 17.21; 95% CI, 6.28–47.14; 12 months: 8.71; 95% CI, 4.03–18.82; until the end of follow up: 5.53; 95% CI, 3.01–10.15). In a sensitivity analysis using date of narcolepsy diagnosis in the NPR instead of symptom onset as extracted from the hospital records, the aHR for narcolepsy within the entire follow-up period was 3.93 (95% CI, 2.47–6.25), slightly lower than the aHR using symptom onset 5.53 (95% CI, 3.01–10.15).The mean time between vaccination and onset of narcolepsy symptoms was 7.6 months (median 5 months; range: 1–28 months).

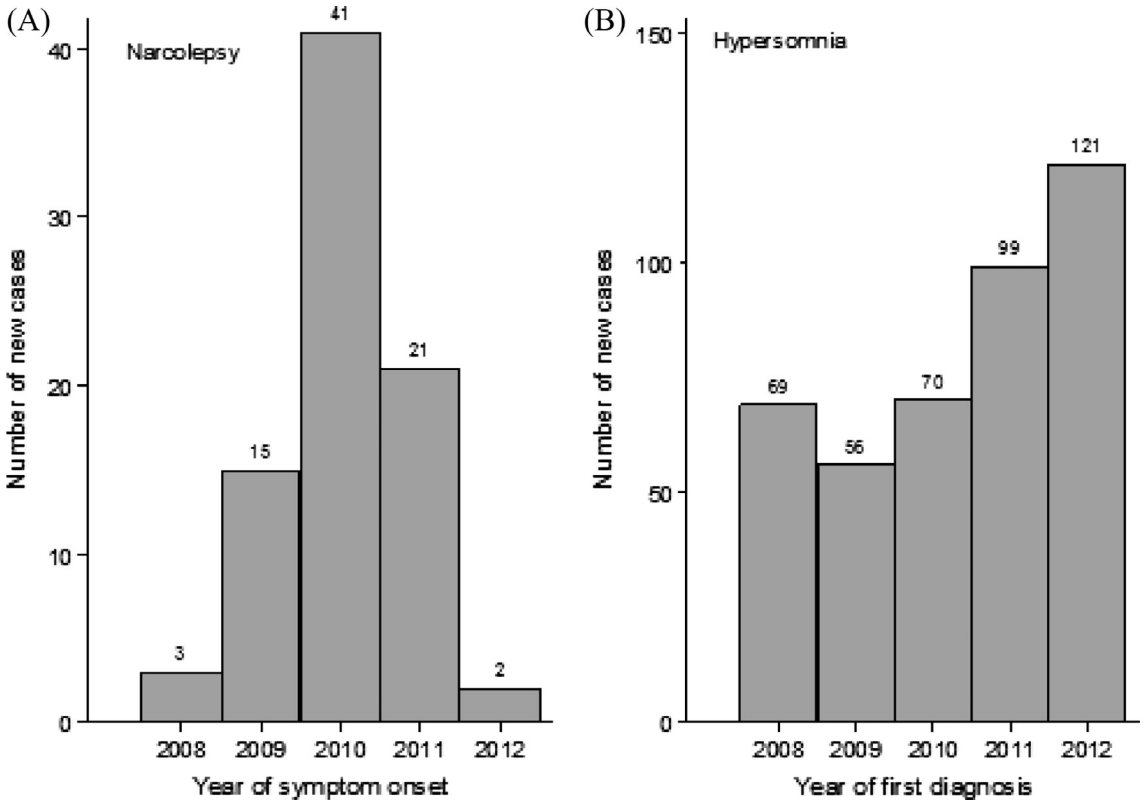


**Fig. 2.** Yearly counts of new onset narcolepsy (ICD10 code G47.4) in 82 children and young adults (A), and new onset hypersomnia (ICD10 code G47.1) in 415 children and young adults (B) in Norway 2008–2012.

**Table 2**
Incidence Rates (IRs) and Adjusted Hazard Ratios (HRs) with 95% Confidence Intervals (CI) for Narcolepsy According to Pandemic Influenza Infection or Vaccination Status.[a]

| Time window | Narcolepsy after influenza[b] | | | Narcolepsy after vaccination[c] | | |
|---|---|---|---|---|---|---|
| | No. of cases | IR[d] | Adjusted HR[e] (95% CI) | No. of cases | IR[d] | Adjusted HR[e] (95% CI) |
| *6 months* | | | | | | |
| No | 69 | 0.11 | 1(ref) | 39 | 0.07 | 1(ref) |
| Yes | 3 | 0.86 | 3.31 (1.01–10.79) | 33 | 0.80 | 17.21 (6.28–47.14) |
| *12 months* | | | | | | |
| No | 69 | 0.11 | 1(ref) | 32 | 0.06 | 1(ref) |
| Yes | 3 | 0.45 | 2.36 (0.73–7.61) | 40 | 0.51 | 8.71 (4.03–18.82) |
| *End of follow up* | | | | | | |
| No | 68 | 0.11 | 1(ref) | 16 | 0.04 | 1(ref) |
| Yes | 4 | 0.18 | 1.96 (0.71–5.37) | 56 | 0.22 | 5.53 (3.01–10.15) |

[a] Shown are hazard ratios based on 72 new cases of narcolepsy during the period October 1, 2009 - December 31, 2012 in the Norwegian population aged 3–29 (N = 1,638,526). Narcolepsy was based on the ICD-10 code G47.4 registered in the Norwegian Patient Register, and validation of diagnoses through review of hospital records.
[b] Influenza-like illness during the peak pandemic period and/or laboratory-confirmed pandemic influenza.
[c] Vaccination against pandemic influenza with Pandemrix.
[d] Per 100,000 person-months.
[e] Stratified Cox proportional-hazards regression model with sex and age (categorized into the groups 3–9 years, 10–19 years, and 20–29 years) as stratification variables and with mutual adjustment for influenza status and vaccination status with the same exposure period.

### 3.4. Hypersomnia

A total of 415 children and young adults were registered with hypersomnia during 2008–2012. Of these, 58.4% were female. The yearly counts of hypersomnia during 2008–2012 were increasing, as illustrated in Fig. 2, panel B.

### 3.5. Influenza and risk of hypersomnia

The HR for hypersomnia after pandemic influenza was significantly increased only for the 6-month exposure period (aHR, 3.13; 95% CI, 1.12–8.76) (Table 3). The mean time between infection and diagnosis was 20.0 months (median: 22 months; range: 2–35 months).

### 3.6. Vaccination and risk of hypersomnia

The HR for hypersomnia after pandemic vaccination exposure was significantly increased only for exposure until end of follow-up (adjusted HR 1.83; 95% CI, 1.44–2.33) (Table 3). The mean time between vaccination and diagnosis of hypersomnia was 22.5 months (median 24 months, range 1–37 months).

**Table 3**
Incidence Rates (IRs) and Adjusted Hazard Ratios (HRs) with 95% Confidence Intervals (CI) for Hypersomnia According to Pandemic Influenza Infection or Vaccination Status.[a]

| Time window | Hypersomnia after influenza[b] | | | Hypersomnia after vaccination[c] | | |
|---|---|---|---|---|---|---|
| | No. of cases | IR[d] | Adjusted HR[e] (95% CI) | No. of cases | IR[d] | Adjusted HR[e] (95% CI) |
| *6 months* | | | | | | |
| No | 295 | 0.48 | 1(ref) | 283 | 0.49 | 1(ref) |
| Yes | 4 | 1.15 | 3.13 (1.12–8.76) | 16 | 0.39 | 1.54 (0.81–2.93) |
| *12 months* | | | | | | |
| No | 294 | 0.48 | 1(ref) | 271 | 0.51 | 1(ref) |
| Yes | 5 | 0.72 | 2.16 (0.87–5.35) | 28 | 0.34 | 1.50 (0.92–2.44) |
| *End of follow up* | | | | | | |
| No | 283 | 0.47 | 1(ref) | 156 | 0.42 | 1(ref) |
| Yes | 16 | 0.74 | 1.64 (0.99–2.72) | 143 | 0.57 | 1.83 (1.44–2.33) |

[a] Shown are hazard ratios based on 305 new cases of hypersomnia during the period October 1, 2009 - December 31, 2012 in the Norwegian population aged 3–29 (N = 1,638,526). Six cases of hypersomnia were registered with first diagnosis in October 2009 and were excluded from the analysis by default (zero follow-up time). Hypersomnia was based on the ICD-10 code G47.1 registered in the Norwegian Patient Register.
[b] Influenza-like illness during the peak pandemic period and/or laboratory-confirmed pandemic influenza.
[c] Vaccination against pandemic influenza with Pandemrix.
[d] Per 100,000 person-months.
[e] Stratified Cox proportional-hazards regression model with sex and age (categorized into the groups 3–9 years, 10–19 years, and 20–29 years) as stratification variables and with mutual adjustment for influenza status and vaccination status with the same exposure period.

### 3.7. Combined effects of exposure to influenza and vaccination

The combined effect of exposure to influenza and vaccination was estimated in a separate analysis, and is presented in Supplementary Table 2. The HR for narcolepsy after exposure to both vaccination and infection was increased as compared to vaccination alone, adjusted HR 18.46 (95% CI, 3.81–89.58) versus adjusted HR 9.11 (95% CI, 4.08–20.37). However, the estimates are based on small numbers, and the confidence intervals are wide and overlapping (Supplementary Table 2). The adjusted HR for hypersomnia after combined exposure to vaccination and infection was also significantly increased as compared to vaccination alone (adjusted HR, 6.46; 95% CI, 1.99–21.03) (Supplementary Table 2).

## 4. Discussion

Using registry data in a complete national population setting, we confirm previous reports of an association between vaccination with Pandemrix and later development of narcolepsy [2–7]. We also report an increased HR for narcolepsy after influenza infection, and for hypersomnia following both influenza infection and vaccination. Narcolepsy cases were confirmed by review of hospital records, and the more than half of all cases fulfilled the criteria for narcolepsy type 1 [1].

The HR for narcolepsy was higher in the first months after vaccination or influenza infection, and declined with longer exposure periods. For hypersomnia, the HR was higher shortly after influenza infection, while HRs following vaccination tended to increase with longer exposure periods. We believe this is the first study to assess risks of narcolepsy and hypersomnia according to length of exposure periods within the same dataset. The change in risk estimates with the length of the exposure periods may possibly explain the differences in estimated risks in previously published papers on pandemic vaccination and narcolepsy [2–7].

Although the association between influenza infection and narcolepsy has not previously been studied in large cohorts with high vaccination coverage, prior observations have suggested increased risks following the influenza pandemic in settings with low (Denmark) or very low (China) vaccination coverage [3,19]. In the four months following the 2009 influenza pandemic peak, the incidence rate of narcolepsy in China sharply increased in a mainly unvaccinated population, and then returned to previous rates in the following timeperiod [20]. Data in the present study showed a similar pattern. The possibility that infections are associated with outbreaks of narcolepsy is also suggested by the seasonal patterns of narcolepsy onset in China, which has revealed a ~6-fold-increase in spring and summer versus winter, suggesting that winter infections such as influenza may trigger the autoimmune attack on hypocretin-producing neurons [19]. However, infections by other infectious agents such as *Streptococci pyogenes* have also been proposed to trigger narcolepsy [21].

A genetic susceptibility to narcolepsy linked to human leukocyte antigen (HLA) DQB1 has been established [22]. Yet, only about 25% of affected monozygotic twins are concordant for narcolepsy, pointing to a significant impact of environmental factors [23]. It is conceivable that common antigens in the influenza A (H1N1) pdm09 virus and the pandemic vaccine Pandemrix may trigger narcolepsy via autoimmune mechanisms [24,25]. The current study may also lend support to the hypothesis that infections can trigger narcolepsy.

The vaccination campaign in Norway coincided with the pandemic influenza peak in 2009. Disentangling the effects of infection and vaccination requires individual exposure measurements. The risk estimates in this type of study seem dependent on the exposure period used, and comparing results from different studies may be difficult. Lack of control for concurrent influenza infection may further make the interpretation difficult.

Since the whole population was included in the current study, selection bias is not expected to have influenced our results. However, underreporting of influenza is present. A clinical diagnosis of influenza during the pandemic was recorded in only 3.6% of the study population while estimates based on national influenza surveillance data suggest a clinical attack rate of approximately 30%, with the highest disease rates among children aged 0–14 years [26]. Many influenza infections may have been subclinical or mild, and only a proportion of symptomatic patients received health care. Thus detection bias due to underreporting of influenza is likely. We demonstrated that most children and young adults were vaccinated *after* the pandemic peak. Hence, it is likely that a large proportion, perhaps up to 30%, had clinical or sub-clinical influenza infection prior to or at the time of vaccination [26]. Consequently, it is plausible that a proportion of patients recorded with narcolepsy or hypersomnia following vaccination were indeed exposed to both influenza and vaccine.

Underreporting of an exposure in an observational study usually biases the relative risks towards no association, as may be the case for influenza in our study. Moreover, misclassification of double exposed individuals to the vaccinated category due to

detection bias could have inflated the HRs for narcolepsy after vaccination, as discussed in two recent simulation studies on influenza vaccination and narcolepsy [27,28]. The same may be true for hypersomnia. Although information on influenza infection was likely to be underreported in the current study, the HRs of narcolepsy and hypersomnia after combined exposure to vaccination and infection was significantly increased.

Registration of vaccination was mandatory [16] and less prone to detection bias. Differential information bias of the association between vaccination and narcolepsy is unlikely during the first 6 months after the pandemic peak, since the excess occurrence of narcolepsy cases first became publicly known in September 2010. Thereafter, massive public attention was drawn to narcolepsy as a possible adverse event following vaccination, thus increasing the risk of differential reporting of vaccinated patients.

Only validated narcolepsy cases were included in the analyses, reducing misclassification. Furthermore, time of symptom onset was extracted from hospital records, possibly reducing misclassification due to recall bias. Review of hospital records showed a positive predictive value of only 60% for narcolepsy according to the Brighton criteria which emphasizes the importance of validating register data, in particular for rare and serious outcomes with long diagnostic trajectories.

The clinical features of hypersomnia may be heterogeneous and of variable severity as previously described [11,29]. For most patients symptoms remain stable over years, although spontaneous remission was described for hypersomnia but not for narcolepsy in one study [30]. Onset may span from childhood onwards. To date, prevalence studies of idiopathic hypersomnia have not been conducted [11]. We are not aware of other publications concerning the association between pandemic influenza/Pandemrix vaccination and hypersomnia, and we can only speculate that this has not been looked for by other researchers. However, anecdotal reports of patients with hypersomnia claiming compensation following Pandemrix vaccination encouraged inclusion of this outcome in the current study – even if validation of the hypersomnia diagnosis in the NPR was not feasible. The diagnosis of hypersomnia was not reviewed in our study, and the accuracy of this diagnosis in the NPR has not been established otherwise. Thus, patients with true narcolepsy may have been misclassified as having hypersomnia upon referral to specialist health care.

The diagnosis of idiopathic hypersomnia requires absence of cataplexy and MSLT showing no or less than two sudden onset REM sleep episodes (SOREMs) [1]. Thus the clinical features of narcolepsy type 2 and idiopathic hypersomnia are very similar. The polysomnographic features of the two conditions are only separated by the SOREM criteria: Less than two in idiopathic hypersomnia, two or more in narcolepsy type 2 [11]. Considering the questionable test-retest reliability of MSLT [31,32], it has been questioned whether there is a difference between the two [11]. The different risk patterns for hypersomnia and narcolepsy according to influenza or vaccination in our study may lend support to the two as different biological entities. However, more than half of all narcolepsy cases in the current study fulfilled the criteria for narcolepsy type 1, which is likely to be caused by destruction of hypocretin-producing neurons and possibly triggered by vaccination or infection. This possible difference in pathogenic mechanism may explain the discrepancy in pattern of response for narcolepsy and hypersomnia. The relatively long observation time in the study allowed thorough examination of suspected narcolepsy cases, but misclassification of patients with true narcolepsy as hypersomnia still cannot be completely ruled out, in particular among patients diagnosed towards the end of the observation time. This may explain why the HR for hypersomnia after vaccination is slightly elevated only at the end of follow up, and to a much lower degree than for narcolepsy.

## 5. Conclusions

In summary, we confirm a statistically significant association between vaccination with Pandemrix and narcolepsy in complete population data. Although a slightly increased HR of narcolepsy and hypersomnia is seen after influenza infection, overall, the role of influenza in the development of narcolepsy and hypersomnia should be viewed with caution due to underreporting of influenza. However, it is remarkable that when both infection and vaccination are present, HRs are increased, suggesting a synergy. Thus, the HR for narcolepsy after vaccination may be inflated since many vaccinated subjects probably were infected before vaccination.

For a full understanding of the association between infection, vaccination and neurological disease a large cohort would need to be established- with repeated exposure assessments, including silent infections, and clinical follow-up of suspected cases. Frequent exposure assessments and long-term commitment of cohort participants are likely to make such a study costly and logistically challenging to undertake. In some countries, like Norway, national health registers represent valuable data sources. However, information on common exposures that only to a small extent requires medical attention, like influenza, is underreported in health registries, and this makes studies of rare outcomes like narcolepsy suboptimal. Still, in our opinion, exploitation of population- based registries and surveillance systems should be continued and efforts to ensure proper data quality strengthened.

## Conflicts of interest

None.

## Authors' contributions

**LT:** Conception and design of the study, preparation of the study protocol, validation of hospital records, interpretation of data and drafting the article.

**IJB:** Preparation of data files, analysis and interpretation of the data, and critically revising the article for important intellectual content.

**NG:** Interpretation of the data and critically revising the article for important intellectual content.

**SG:** Interpretation of the data and critically revising the article for important intellectual content.

**CS:** Interpretation of the data and critically revising the article for important intellectual content.

**PM:** Design, interpretation of the data, drafting and critically revising the article for important intellectual content.

**SEH:** Conception and design of the study, preparation of the analyses plan, validation of hospital records, interpretation of data and drafting the article.

All authors have approved the final version of the manuscript.

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## Disclaimers

Data from the Norwegian Patient Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

Data from the Norwegian Immunisation Registry, SYSVAK have been used in this publication. The interpretation and reporting of

these data are the sole responsibility of the authors, and no endorsement by the Norwegian Immunisation Registry is intended nor should be inferred.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.02.053.

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