Increasing risk of prosthetic joint infection after total hip arthroplasty

2,778 revisions due to infection after 432,168 primary THAs in the Nordic Arthroplasty Register Association (NARA)

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Background and purpose The risk of revision due to infection after primary total hip arthroplasty (THA) has been reported to be increasing in Norway. We investigated whether this increase is a common feature in the Nordic countries (Denmark, Finland, Norway, and Sweden).

Materials and methods The study was based on the Nordic Arthroplasty Register Association (NARA) dataset. 432,168 primary THAs from 1995 to 2009 were included (Denmark: 83,853, Finland 78,106, Norway 88,455, and Sweden 181,754). Adjusted survival analyses were performed using Cox regression models with revision due to infection as the endpoint. The effect of risk factors such as the year of surgery, age, sex, diagnosis, type of prosthesis, and fixation were assessed.

Results 2,778 (0.6%) of the primary THAs were revised due to infection. Compared to the period 1995–1999, the relative risk (with 95% CI) of revision due to infection was 1.1 (1.0–1.2) in 2000–2004 and 1.6 (1.4–1.7) in 2005–2009. Adjusted cumulative 5–year revision rates due to infection were 0.46% (0.42–0.50) in 1995–1999, 0.54% (0.50–0.58) in 2000–2004, and 0.71% (0.66–0.76) in 2005–2009. The entire increase in risk of revision due to infection was within 1 year of primary surgery, and most notably in the first 3 months. The risk of revision due to infection increased in all 4 countries. Risk factors for revision due to infection were male sex, hybrid fixation, cement without antibiotics, and THA performed due to inflammatory disease, hip fracture, or femoral head necrosis. None of these risk factors increased in incidence during the study period.

Interpretation We found increased relative risk of revision and increased cumulative 5–year revision rates due to infection after primary THA during the period 1995–2009. No change in risk factors in the NARA dataset could explain this increase. We believe that there has been an actual increase in the incidence of prosthetic joint infections after THA.

The outcome of hip replacement surgery and the survival of implants have improved during the last decades (Herberts and Malchau 2000, Liu et al. 2009, Fevang et al. 2010). However, an increase in the risk of revision due to infection after THA has also been reported in recent years (Kurtz et al. 2008, Dale et al. 2009, Pedersen et al. 2010b). We wanted to assess whether the increase in risk of revision due to infection is a common feature in the Nordic countries, and we therefore assessed time trends and risk factors for revision due to infection after primary total hip arthroplasty (THA) in the Nordic countries (Denmark, Finland, Norway, and Sweden). The aim was to compare revision rates due to infection in different time periods and different patient and implant groups, and to investigate factors that influence the risk of revision due to infection.

Materials and methods

The Nordic Arthroplasty Register Association dataset

The NARA dataset contains merged individual-based data from the Danish, Finnish, Norwegian, and Swedish arthroplasty reg-

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isters (Herberts et al. 1989, Havelin et al. 2000, Lucht 2000, Puolakka et al. 2001, Malchau et al. 2005, Havelin et al. 2009). In each register, the data selected were transformed according to a common set of definitions, and revisions were linked to the primary procedures. The data were de-identified nationally before the anonymous data were merged into the NARA dataset. The data were treated in full confidentiality and in compliance with the regulations of each country (Havelin et al. 2009).

The inclusion criteria in the present study were primary THAs and first revisions from the period 1995 through 2009, with complete information on the following parameters: year of primary surgery and first revision, age, sex, diagnosis (osteoarthrosis (OA), inflammatory hip disease, hip fracture, childhood hip disease, femoral head necrosis, or other diagnoses), prosthesis (monoblock or modular), and type of fixation (uncemented, cemented, hybrid, or inverse hybrid, with plain or antibiotic-loaded cement). Primary THA was defined as the first total hip prosthesis regardless of cause of the arthroplasty. The endpoint was revision due to infection, and revision was defined as removal or exchange of the whole or part(s) of the prosthesis. Infection as the cause of revision was determined and reported by the surgeon immediately after surgery, based on the preoperative clinical manifestations and samples in addition to peroperative evaluation. The national datasets were harmonized according to these definitions. Of the 459,540 primary arthroplasties in the NARA dataset, 7,450 resurfacing arthroplasties were not considered as THAs. Of the 452,090 THAs, 3,397 were excluded due to unknown type of fixation, as were 16,525 THAs due to incomplete information on the risk factors. 432,168 THAs met the inclusion criteria. Denmark contributed 83,853 primary THAs, Finland 78,106, Norway 88,455, and Sweden 181,754 (Table 1).

Table 1. Patient and procedure characteristics for the primary THAs included, and number of primary THAs excluded over the 3 time periods

	1995–1999	2000–2004	2005–2009	1995–2009
Number of THAs included	113,280	147,823	171,065	432,168
Age (%)				
<40 years	2	1	1	1
40–59 years	17	18	17	17
60–69 years	29	29	32	30
70–79 years	38	37	35	36
80–89 years	14	15	15	15
≥90 years	1	1	1	1
Sex (%) Female	63	62	61	61
Diagnosis (%)				
Osteoarthritis	76	80	83	80
Hip fracture	10	7	6	8
Inflammatory disease	5	4	2	4
Childhood hip disease	4	4	3	3
Femoral head necrosis	2	2	2	2
Other diagnoses	2	3	3	3
Prosthesis (%)				
Monoblock	22	10	2	10
Modular	78	90	98	90
Fixation (%)				
Uncemented	13	16	30	21
Cemented	76	71	56	67
Hybrid	10	10	6	9
Inverse hybrid	1	3	8	4
Cement (%)				
No cement	13	16	30	21
With antibiotics	71	79	69	73
Without antibiotics	15	5	1	6
Country (%)				
Denmark	14	20	22	21
Norway	23	21	19	20
Sweden	45	42	41	42
Finland	19	17	18	18
Number of THAs excluded	10,540	3,303	6,169	9,922 (4.4%)

Statistics

Descriptive statistics were used for presentation of the patient and procedure characteristics. Adjusted Cox regression analyses were performed to assess relative risk of revision due to infection and to estimate adjusted cumulative 5-year probability (risk) of revision. Unadjusted cumulative 5-year risks of revision due to infection were estimated by the Kaplan-Meier (KM) method. The study population was divided into 5-year periods (1995–1999, 2000–2004, and 2005–2009). The cases were observed until first revision, death, emigration, or December 31, 2010. We also investigated changes in the revision rates due to deep infection as a function of the year of operation, to give a graphical display of the relationship based on a generalized additive model for survival data (Hastie and Tibshirani 1990). Adjusted hazard rate ratios, as a measure of relative risk, were estimated, with 95% confidence intervals (CIs) for time periods and risk factors. In the Cox analyses we adjusted for age, sex, diagnosis, modularity of the prosthesis, and fixation, and the influence on revision risk of each of these factors was assessed. Separate Cox analyses were performed on a homogenous subgroup of hips with cemented modular THAs with antibiotics in the cement on patients with OA, as this combination was common throughout the 3 time periods in all 4 countries.

The Cox survival analyses were performed with 1–16 years of follow-up, but the last time period had only 1–6 years of follow-up. To ensure that there was similar follow-up for operations in all 3 time periods, we performed additional analyses with follow-up restricted to 1–6 years for each time period. In addition, we performed separate time trend analyses of revision due to infection for men and women, all age groups, and groups of diagnoses separately. Also, the risk factors were studied in each country separately. Finally, we assessed the risk factors separately within each of the 3 time periods to

Table 2. Relative risk of revision due to infection of primary THAs in the NARA with 1–16 years of follow–up. Adjusted for age, sex, diagnosis, prosthesis, and cement

	Period	Number of THAs included	Number of THAs revised due to infection	Adjusted risk ratio for revision due to infection	95% confidence interval	p–value
All THAs	1995–1999	113,280	778	1		
	2000–2004	147,823	937	1.1	1.0–1.2	0.03
	2005–2009	171,065	1,063	1.6	1.4–1.7	<0.001
Uncemenxted THAs	1995–1999	15,177	87	1		
	2000–2004	23,553	147	1.4	1.0–1.8	0.03
	2005–2009	51,445	308	1.9	1.5–2.5	<0.001
Cemented THAs	1995–1999	86,177	538	1		
	2000–2004	105,421	641	1.2	1.1–1.3	0.006
	2005–2009	96,455	619	1.7	1.5–2.0	<0.001
Hybrid THAs	1995–1999	11,369	149	1		
	2000–2004	15,163	125	0.8	0.6–1.0	0.02
	2005–2009	10,390	63	0.8	0.6–1.1	0.2
Inverse hybrid THAs	1995–1999	556	4	1		
	2000–2004	3,685	24	1.3	0.4–4.0	0.6
	2005–2009	12,775	73	1.6	0.5–4.6	0.4
Cemented modular THAs with antibiotics in cement inserted due to OA [a]	1995–1999	37,848	208	1		
	2000–2004	69,052	374	1.1	0.9–1.3	0.2
	2005–2009	75,929	467	1.7	1.4–2.0	<0.001

[a] Adjusted for age and sex.

minimize time-dependent confounding. Additional Cox analyses with the endpoints revision due to aseptic loosening and revision for any cause were performed to relate these to our findings on revision due to infection.

The analyses were performed in accordance with the guidelines for statistical analyses of arthroplasty register data (Ranstam et al. 2011). The proportional-hazard assumptions of the Cox survival analyses were not completely fulfilled. We therefore assessed the proportionality of the main risk factors by smoothed Schoenfeld residuals (Figure 3) (Ranstam et al. 2011). This resulted in assessment of the risk factors before and after 1 year, since adjusted revision rates of the 3 time periods were not fully proportional. Potential overestimation of incidence of revision due to infection through the effect of competing risks (death and revision due to causes other than infection) was assessed by the cumulative incidence function (Gillam et al. 2010). The 3.9% of THAs that were revised for causes other than infection and the 21% of THA patients who died during the follow-up had a negligible effect on the Cox analyses.

Bilateral THAs are not independent observations, but were included. The extent of bilaterality was estimated to be 18% and the incidence of revision due to infection was 0.6% in both the first and second hip. Only 0.05% of the bilateral THAs were identified to have had revisions due to infection in both hips. We therefore considered bilaterality to have a negligible influence on the results (Lie et al. 2004, Ranstam and Robertsson 2010, Ranstam et al. 2011).

Values of $p < 0.05$ were considered to be statistically significant. SPSS software version 18.0 and the R statistical software package were used for the analyses.

Results

2,778 primary THAs (0.6%) were revised due to deep infection. The cumulative 5-year revision rate due to infection, adjusted for year of primary surgery, was 0.62% (0.60–0.65) for the study population and 0.99% (0.83–1.15) for the excluded THAs (4.4% of the total). The implants at use had changed during the study period. In the last 5-year period, there were more uncemented THAs and inverse hybrid THAs and nearly all of the cemented THAs were modular and inserted with cement containing antibiotics (Table 1). There were only minor changes in the distribution of patient-related risk factors over the study period, with the exception that fewer THAs were performed due to inflammatory disease and hip fracture later in the study period (Table 1).

Time trend of revision due to infection

The risk of revision due to infection increased in the period 2005–2009 relative to the period 1995–1999 in the total study population (Table 2; Figures 1 and 2), and in each of the 4 countries separately (Denmark: RR = 1.3 (CI 1.0–1.6); Norway: RR = 1.7 (1.2–2.3); Sweden: RR = 1.5 (1.2–1.9); and Finland: RR = 1.2 (1.0–1.5)). For the period 2000–2004, the risk of revision due to infection only increased in Norway (RR = 1.3 (1.1–1.6)). The overall cumulative 5-year revision rate due to infection also increased, despite the fact that the revision rate for the period 2005–2009 might be an underestimate due to incomplete 5-year follow-up (Table 3 and Figure 1). The subgroup of cemented modular THAs with antibiotic-loaded bone cement in OA patients showed similar results (Tables 2 and 3; Figures 1 and 2).

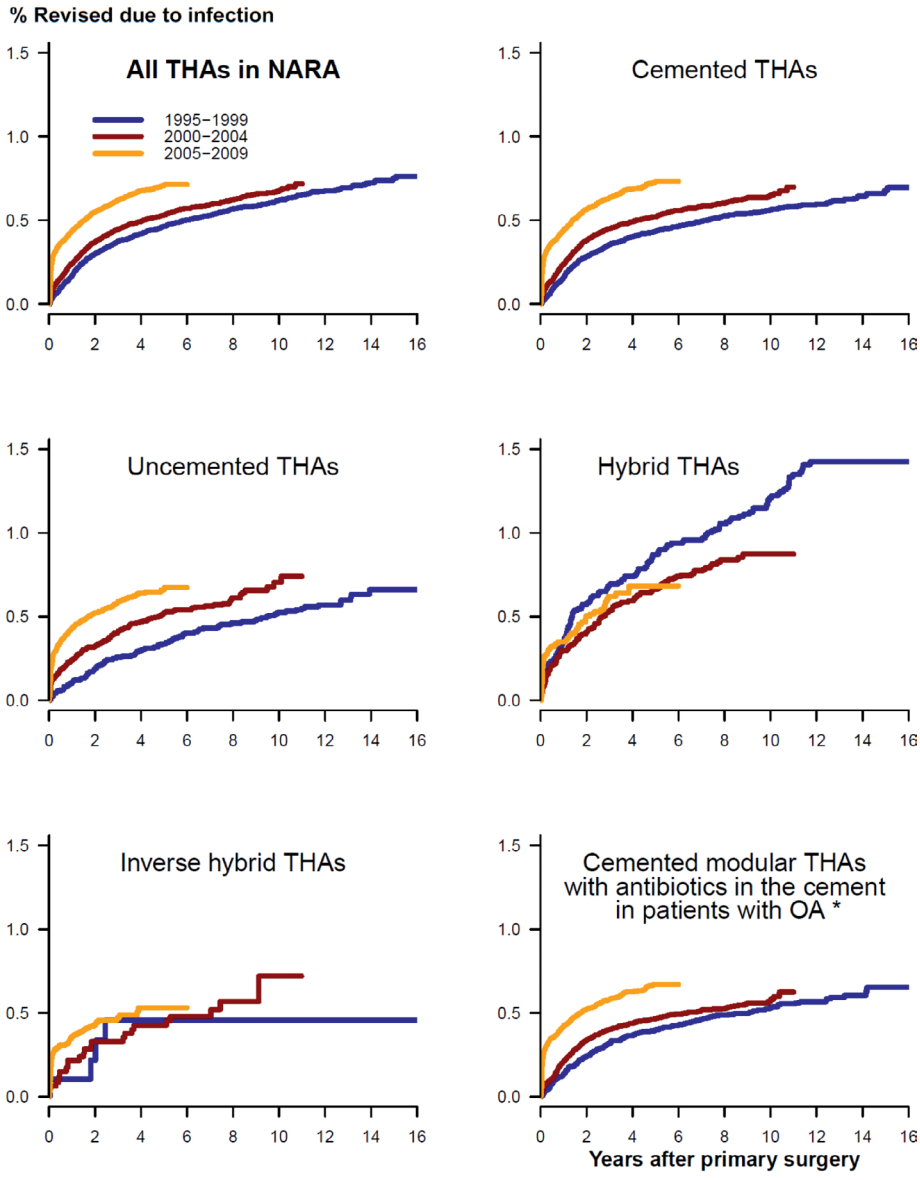

Figure 1. Adjusted cumulative revision rates for THAs revised due to infection in 3 time periods of primary surgery, for all THAs (upper left panel) and 5 subgroups of THAs. Adjusted for age, sex, diagnosis, prosthesis, and cement. *Adjusted for age and sex only.

The entire increase in risk of revision due to infection occurred within 1 year of primary surgery, and most notably within the first 3 months after surgery (Table 4; Figures 1 and 3). The increased risk of revision due to infection was found for cemented and uncemented THAs, but not for hybrid THAs and inverse hybrid THAs (Table 2; Figures 1 and 2). The increase in risk of revision due to infection was more gradual through the time periods for uncemented THAs than for cemented THAs, where the main increase in relative risk of revision and cumulative 5-year revision rate was in the last time period (Tables 2 and 3; Figures 1 and 2).

The risk of revision due to infection increased similarly for men and women, in all age groups and for the different diagnoses, as well as for the excluded cases.

Time trend of revision due to aseptic loosening and revision for any cause

The adjusted cumulative 5-year revision rate due to aseptic loosening was lower in 2000–2004 and 2005–2009 than in 1995–1999, but the last time period did not have complete 5-year follow-up and would have been an underestimate (Table 3). For uncemented THAs, the cumulative 5-year revision rate due to aseptic loosening did not improve during the study period (Table 3). For revisions due to any cause, there was no improvement in cumulative 5-year revision rate during the study period, except for hybrid THA, despite the incomplete 5-year follow-up in 2005–2009 (Table 3). Compared to other methods of fixation, cemented THA had the lowest cumulative 5-year revision rate for any cause in 2005–2009 (Table 3).

Risk factors for revision due to infection

Male sex and THA performed due to inflammatory disease, hip fracture, or femoral head necrosis were the patient-related risk factors associated with increased risk of revision due to infection (Table 5). Implant-related risk factors that increased the relative risk of revision due to infection were hybrid fixation and plain bone cement (Table 5). The findings were similar when we assessed the risk factors within each time period separately and before and after 1 year after primary surgery. The exception was patients of advanced age at primary THA, who had a higher risk of revision due to infection within the first year after surgery, whereas they had a lower risk of revision due to infection more than 1 year postoperatively.

Discussion

Our main finding was the higher risk of revision due to infection after primary uncemented and cemented THAs in the 4 Nordic countries for the period 2005–2009 than for the period

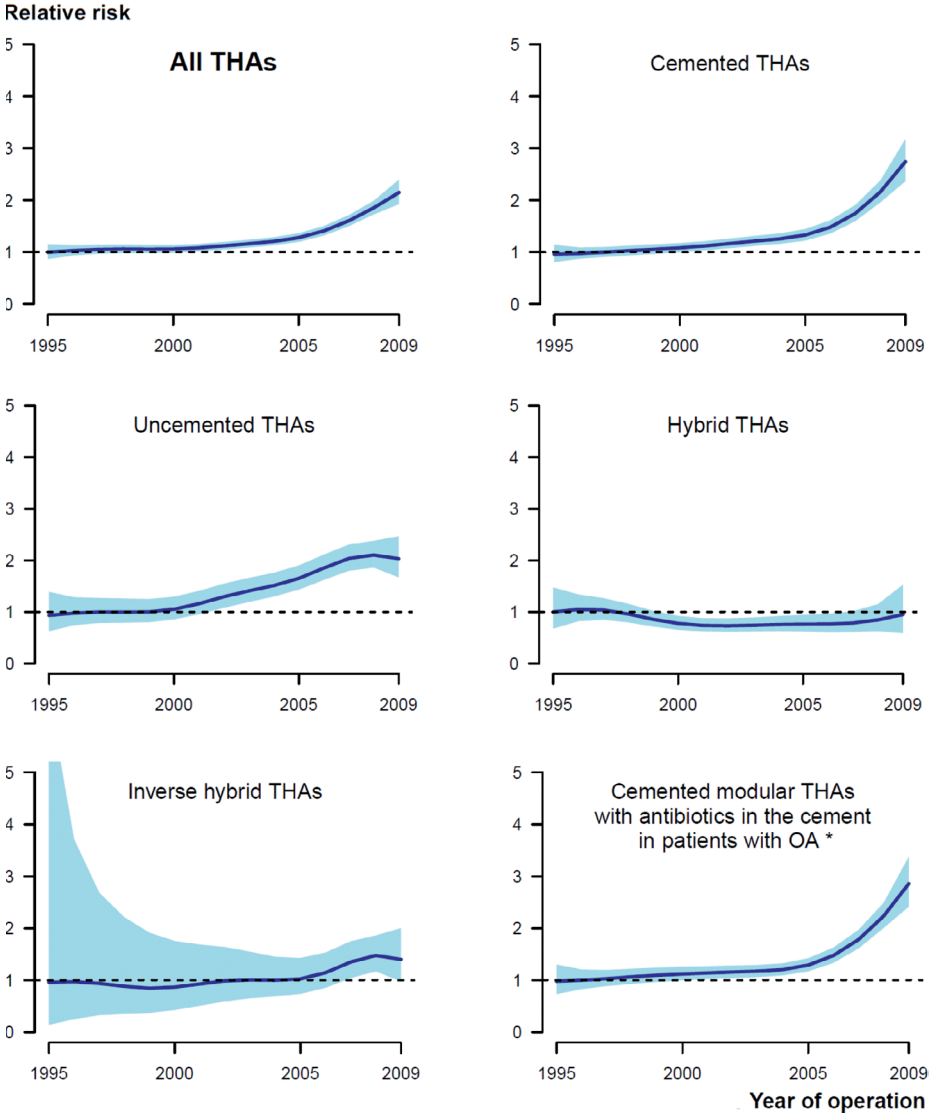

Figure 2. Graphical display of the relationship between year of primary surgery and relative risk of revision due to infection (with 95% CI), for all THAs (upper left panel) and 5 subgroups of THAs. The broken lines represent no difference in relative risk from the beginning of the period (RR = 1). Adjusted for age, sex, diagnosis, prosthesis, and cement. *Adjusted for age and sex.

1995–1999. This confirms earlier reports from Norway and Denmark (Dale et al. 2009, Pedersen et al. 2010b). The cumulative 5-year revision rate due to infection was also higher in 2005–2009 than in the previous 2 time periods. This was the case even though the revision rates for 2005–2009 probably were underestimates due to the incomplete 5-year follow-up, and they might therefore have been expected to be even higher.

None of the risk factors that we assessed could explain the increased risk of revision due to infection. The incidence of unfavorable risk factors (male sex, hybrid fixation, cement without antibiotics, and THA performed due to inflammatory disease, hip fracture, or femoral head necrosis) did not increase during the study period. In addition, these confounders were adjusted for in the analyses. An increased incidence of prosthetic joint infection would therefore have to be caused by factors that are not registered in the NARA dataset. These may include changes in patient-related factors (i.e. more comorbidity), changes in microbiology (i.e. increased bacterial virulence or more resistant strains), or changes in surgery-related factors (i.e. duration of surgery or changed surgical technique).

The common NARA dataset contains only limited information on comorbidity, which is a well-documented risk factor for infection after THA (Ridgeway et al. 2005, Pulido et al. 2008, Pedersen et al. 2010b, Dale et al. 2011). If THA was performed on more patients with poor health in the later parts of the study period, an increased incidence of prosthetic joint infections could result. In Norway, the comorbidity at THA increased during 2005–2009 (The Norwegian Arthroplasty Register 2010). The incidence of specific comorbidities associated with increased risk of infection after THA, like obesity and diabetes, is increasing in several countries (Pedersen et al. 2010a, Danaei et al. 2011, Haverkamp et al. 2011, Mraovic et al. 2011, Doak et al. 2012, Iorio et al. 2012). Given that the THA patients reported to the NARA are representative of the general population, an increased incidence of prosthetic joint infections requiring revision could result.

Surgery-related risk factors such as duration of surgery, and timing and type of systemic antibiotic prophylaxis are also not included in the NARA dataset. However, both short and long duration of surgery have been shown to be risk factors for infection (Ridgeway et al. 2005, Pulido et al. 2008, Dale et al. 2009, Pedersen et al. 2010b, Dale et al. 2011). Less compliance to guidelines for optimal systemic prophylaxis could also have contributed to an increased incidence of prosthetic joint infections, as could an increase in bacterial resistance to antibiotic prophylaxis (Kerttula et al. 2007, Stefansdottir et al. 2009a, b, Lutro et al. 2010). Finally, changes in operation room ventilation or changed adherence to guidelines of prophylactic routines may also have influenced the trend of revision due to infection (National Institute of Health and Clinical Excellence (NICE) 2008, Dale et al. 2009).

Table 3. Adjusted cumulative 5-year revision rates of primary THAs in the NARA. Adjusted for age, sex, diagnosis, prosthesis, and cement

	Period	Number of THAs included	Cumulative 5-years revision rate							
			Kaplan–Meier infection		Adjusted infection		Adjusted aseptic loosening		Adjusted all revisions	
All THAs	1995–1999	113,280	0.54	(0.49–0.58)	0.46	(0.42–0.50)	1.41	(1.34–1.49)	3,34	(3.22–3.45)
	2000–2004	147,823	0.57	(0.53–0.61)	0.54	(0.50–0.58)	0.81	(0.77–0.86)	3.01	(2.92–3.10)
	2005–2009 [b]	171,065	0.73	(0.68–0.77)	0.71	(0.66–0.76)	1.00	(0.93–1.07)	3.30	(3.19–3.41)
Uncemented THAs	1995–1999	15,177	0.36	(0.26–0.45)	0.34	(0.25–0.44)	1.32	(1.13–1.50)	4.39	(4.05–4.72)
	2000–2004	23,553	0.55	(0.45–0.65)	0.52	(0.43–0.61)	0.85	(0.73–0.97)	4.28	(4.02–4.54)
	2005–2009 [b]	51,445	0.70	(0.61–0.78)	0.65	(0.57–0.74)	1.21	(1.08–1.34)	4.24	(4.02–4.45)
Cemented THAs	1995–1999	86,177	0.51	(0.47–0.56)	0.43	(0.38–0.48)	1.34	(1.25–1.43)	2.82	(2.70–2.94)
	2000–2004	105,421	0.56	(0.51–0.60)	0.52	(0.48–0.57)	0.74	(0.68–0.79)	2.53	(2.43–2.63)
	2005–2009 [b]	96,455	0.74	(0.68–0.81)	0.74	(0.67–0.80)	0.85	(0.77–0.94)	2.93	(2.80–3.07)
Hybrid THAs	1995–1999	11,369	0.94	(0.76–1.12)	0.88	(0.70–1.06)	1.82	(1.55–2.09)	4.92	(4.50–5.34)
	2000–2004	15,163	0.72	(0.58–0.85)	0.67	(0.53–0.80	0.98	(0.81–1.14)	3.79	(3.48–4.10)
	2005–2009 [b]	10,390	0.72	(0.54–0.90)	0.67	(0.50–0.85)	1.00	(0.75–1.25)	3.86	(3.41–4.31)
Inverse hybrid THAs	1995–1999	556	0.77	(0.02–1.51)	0.36	(0–1.38)	2.36	(0.97–3.75	5.59	(3.65–7.54)
	2000–2004	3,685	0.53	(0.29–0.77)	0.34	(0–1.27)	1.64	(1.19–2.09)	3.98	(3.31–4.64)
	2005–2009 [b]	12,775	0.66	(0.50–0.83)	0.43	(0–1.58)	1.37	(1.02–1.72)	3.67	(3.20–4.14)
Modular THAs with antibiotics in cement in patients with OA [a]	1995–1999	37,848	0.43	(0.36–0.49)	0.40	(0.33–0.46)	1.18	(0.67–1.69)	2.60	(2.44–2.77)
	2000–2004	69,052	0.49	(0.44–0.55)	0.47	(0.41–0.52)	0.69	(0.39–0.99)	2.21	(2.10–2.32)
	2005–2009 [b]	75,929	0.71	(0.64–0.77)	0.67	(0.60–0.73)	0.78	(0.44–1.12)	2.60	(2.46–2.75)

[a] Adjusted for age and sex.
[b] Cumulative 5-year revision rates probably were underestimates due to incomplete 5-year follow-up.

Table 4. Adjusted relative risks of revision due to infection for 4 different time intervals after primary surgery, for the 3 time periods. Adjusted for age, sex, diagnosis, prosthesis, and cement

Time after primary surgery	Number of THAs included	Number of THAs revised due to infection	Adjusted risk ratio for revision due to infection	95% CI	p–value
0–3 months					
1995–1999	113,280	74	1		
2000–2004	147,823	175	1.9	1.4–2.4	<0.001
2005–2009	171,065	535	4.8	3.7–6.2	<0.001
3–12 months					
1995–1999	111,607	142	1		
2000–2004	145,625	206	1.3	1.0–1.6	0.05
2005–2009	168,019	216	1.2	1.0–1.5	0.09
1–2 years					
1995–1999	109,178	164	1		
2000–2004	142,589	195	1.1	0.9–1.3	0.6
2005–2009	164,758	175	1.0	0.8–1.3	0.9
> 2 years					
1995–1999	105,338	398	1		
2000–2004	138,270	361	0.9	0.8–1.1	0.5
2005–2009	126,131	137	0.9	0.7–1.1	0.2

Other confounders not reported to the NARA may have contributed to an increase in reporting of revision due to infection to the registers without reflecting a corresponding increase in true incidence of prosthetic joint infection. Such confounders could be improved reporting of revisions due to infection, changes in revision policy and in the threshold of revision (i.e. new surgical methods), or changes in diagnostics (i.e. improved microbiological detection methods and changed definitions) (Dale et al. 2009, Pedersen et al. 2010b).

Since 2000, in Norway there has been an increase in the reporting of minor revision procedures, such as soft tissue debridement procedures with exchange of removable parts of modular implants and retention of the femoral stem and acetabular cup (Engesæter et al. 2011). Such procedures were reported to the registers as revision procedures because prosthesis parts were exchanged. These minor revisions may have different indications or a lower threshold to be performed than full exchange revisions. Such minor revisions may also be performed and reported earlier postoperatively than full exchange revisions. This may be the reason for the increased risk of revision due to infection in the first year after primary surgery, as found for the latter 2 time periods. In addition, similar operations performed on monoblock prostheses would not be reported because heads and liners were not exchanged. We adjusted for this potential under-reporting of infected monoblock prostheses in the analyses. In addition, the minor partial revisions were most likely used as alternatives to complete exchange procedures

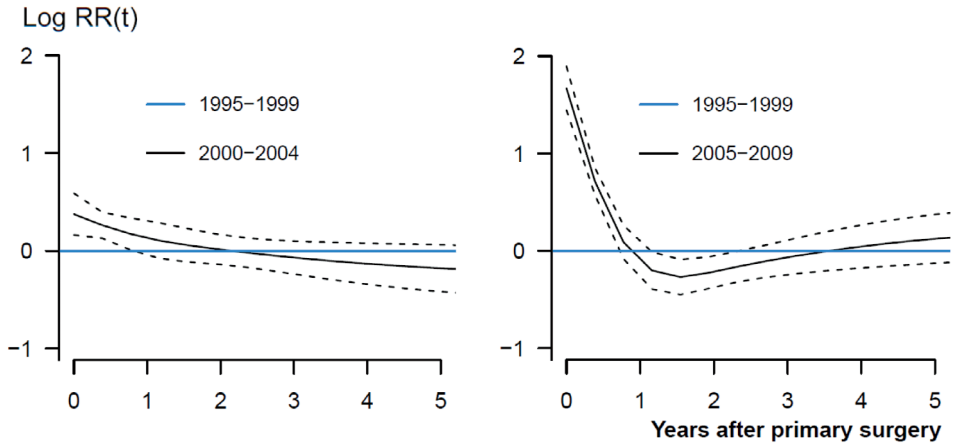

Figure 3. A graphical display of the relationship between relative risk of revision due to infection and time after primary THAs for the period 2000–2004 (left panel) and 2005–2009 (right panel) compared to 1995–1999 (blue lines). Smoothed Schoenfeld residuals adjusted for age, sex, diagnosis, prosthesis and cement (solid lines) with 95% confidence intervals (broken lines).

rather than alternatives to no revision at all. This is supported by the finding of a higher risk of revision due to infection in 2005–2009 than in 1995–1999 both for the uncemented THAs, which were all modular, and for the more homogenous subgroup of modular THAs inserted with cement containing antibiotics in patients with OA. In addition, in Norway the incidence of major revision due to infection increased during 1995–2009 as well (Engesæter et al. 2011). Thus, we do not think that increased use of modular implants and the changes in revision policy could explain the increased risk of revision due to infection.

There have been improvements in the diagnostics of prosthetic joint infections. Some bacteria such as coagulase-negative staphylococci have been increasingly acknowledged for their pathogenicity (von Eiff et al. 2006). In addition, improvements in bacterial sampling and identification may also have increased the number of infections being identified preoperatively (Trampuz and Widmer 2006, Moojen et al. 2007). The clinical presentation of an aseptic loosening and a low-grade periprosthetic infection may also be similar (Tunney et al. 1998, Ince et al. 2004, Moojen et al. 2010). If

Table 5. Adjusted relative risks and adjusted cumulative 5–year revision rates for risk factors for revision due to infection. All risk factors were adjusted mutually for the other risk factors in addition to the year of primary surgery. Follow–up in the risk analyses was 1–16 years

	Number of THAs included	Number of THAs revised due to infection	Adjusted risk ratio for revision due to infection	95% confidence interval	p–value	Adjusted cumulative 5-years revision rate, infection
Age (years)						
<40	5,590	39	1			0.47
40–51	74,107	515	1.1	0.8–1.5	0.6	0.59
60–69	129,134	854	1.1	0.8–1.5	0.7	0.58
70–79	157,292	1,021	1.1	0.8–1.5	0.6	0.62
80–89	63,034	337	0.9	0.7–1.3	0.8	0.52
≥90	3,011	12	0.7	0.4–1.4	0.3	0.32
Sex						
Female	266,42	1,312	1			0.46
Male	165,748	1,466	1.9	1.8–2.1	<0.001	0.87
Diagnosis						
Osteoarthritis	345,925	2,090	1			0.54
Hip fracture	33,572	327	2.1	1.9–2.4	<0.001	1.12
Inflammatory disease	15,771	118	1.4	1.1–1.7	0.001	0.72
Childhood hip disease	14,983	80	0.9	0.7–1.2	0.6	0.51
Femoral head necrosis	9,671	92	1.7	1.4–2.1	<0.001	0.87
Other diagnoses	12,246	71	1.3	1.0–1.6	0.06	0.65
Prosthesis						
Modular	388,371	2,475	1			0.58
Monoblock	43,797	303	1.1	1.0–1.3	0.09	0.69
Fixation						
Uncemented	90,177	542	1			0.54
Cemented	288,053	1,798	1.1	1.0–1.2	0.09	0.58
Hybrid	36,922	337	1.6	1.4–1.8	<0.001	0.79
Inverse hybrid	17,016	101	1.0	0.8–1.3	0.7	0.53
Cement						
With antibiotics	316,072	1,997	1			0.58
Without antibiotics	25,921	239	1.5	1.3–1.8	<0.001	0.96

knowledge and awareness changed during the study period, there may have been a corresponding change in reporting of infection as the cause of the revision. Unexpectedly positive peroperative bacterial samples would be identified postoperatively and would not be reported to the registers. Some prosthetic joint infections may therefore have been erroneously registered as aseptic loosening in the NARA, but possibly to a lesser extent in the later stages of the study period due to improvements in diagnostics.

Our finding of increased risk of revision due to infection, which is the definition of infection used by the NARA, most probably reflects a true increase in incidence of prosthetic joint infections. To our knowledge, there have been no publications on time trends of the incidence of prosthetic joint infections after primary THA. Kurtz et al. (2008) reported a 2-fold increase in overall incidence of deep infection after THA from 0.66% in 1990 to 1.23% in 2004. This study on "total infection burden" was based on aggregated data, without any linkage between primary THA and revision after discharge and with both primary and revision arthroplasty included in the analyses. For primary THAs only, the authors found a reduced incidence of infection, most probably due to shorter length of hospital stay.

Another manifestation of infection after THA is surgical site infection, which a subject of interest in large infection surveillance programs. The definition of surgical site infection is wider than those of prosthetic joint infection and revision due to infection: the risk pattern is different and the follow-up is more limited than in arthroplasty registers (HELICS 2004, Dale et al. 2011). It may be that the treatment strategy for early postoperative soft tissue infections has become more aggressive in recent years, resulting in an increased revision rate. However, only one fifth of the surgical site infections reported to the Norwegian Surveillance System for Healthcare Associated Infections after primary THAs were reported to the Norwegian Arthroplasty Register for revisions due to infection in the period 2005–2009 (Dale et al. 2011). Both revision due to infection and surgical site infection will be surrogate endpoints of true prosthetic joint infections (Parvizi et al. 2011).

The Dutch National Nosocomial Surveillance Network (PREZIES) reported a decrease in surgical site infections after primary THA between 1996 and 2006 (Mannien et al. 2008), as did the British mandatory surveillance of SSI between 2004 and 2010 (Health Protection Agency 2011). Capture of surgical site infections is highly dependent on length of stay after primary THA or type and length of post-discharge surveillance (Huotari and Lyytikainen 2006). For instance, low-grade prosthetic joint infections, presenting as pain and loosening of the implant at a later stage, will generally be missed in surveillance programs for surgical site infection. The reported decrease in the incidence of surgical site infections may therefore be due to shorter length of stay and limited post-discharge surveillance, and not to a reduction in the incidence of prosthetic joint infections in need of revision (Mannien et al. 2008, Health Protection Agency 2011).

A previous study from Norway found that uncemented THAs had a higher risk of revision due to infection than cemented THAs (Dale et al. 2009). A study from Denmark, in contrast, found that cemented THAs had higher risk of revision due to infection than uncemented THAs (Pedersen et al. 2010b). In the present study, the overall risk of revision due to infection was similar for cemented, inverse hybrid, and uncemented THAs.

We found an incidence of revision due to infection of 0.6%; it is therefore a relatively rare complication after THA. Large populations are required for the study of time trends and risk factors for such rare events. The large NARA dataset offers an opportunity for in-depth studies of revision due to infection even in subgroups with sufficient power. The data are prospective and have a high degree of completeness (Soderman et al. 2000, Pedersen et al. 2004, Espehaug et al. 2006). The completeness of the NARA dataset and the small proportion of cases excluded in the present study (4.4%) also indicate that there was minimal selection bias, even if the relative risk of revision due to infection was higher in the excluded group. The time trend of revision due to infection was similar for the included cases and the excluded cases. The number of variables in the NARA dataset is limited, however, and even though we adjusted for several well-known confounders in our analyses, unmeasured confounding would still be a problem.

Considering the size and quality of the NARA dataset, and the adjustment for several clinically important risk factors, we believe that there has been a true increase in the risk of prosthetic joint infections. The largest increase in relative risk of revision due to infection was for uncemented THAs, but the overall risk of revision due to infection was similar for cemented, uncemented, and inverse hybrid THAs. Male sex, hybrid fixation, cement without antibiotics, and THA performed due to inflammatory disease, hip fracture, or femoral head necrosis were risk factors for revision due to infection.

HD and AMF performed the analyses. HD wrote the manuscript. All the authors contributed to interpretation of the analyses and to critical revision of the manuscript.

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