

Is decreasing mortality in total hip and knee arthroplasty patients dependent on patients' comorbidity?

A Danish nationwide, population-based cohort study (1996–2013)

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Background and purpose — Mortality after primary total hip and knee arthroplasty (THA and TKA) has declined, and the proportion of THA and TKA patients with comorbid conditions has increased. We therefore wanted to examine changes in comorbidity burden over time and the impact of comorbid on mortality following primary total hip and knee arthroplasty in patients with osteoarthritis.

Patients and methods — We used the Danish arthroplasty registers to identify THA and TKA patients from 1996 through 2013. From administrative databases, we collected data on pre-surgery hospital history for all patients, which were used to calculate the Charlson comorbidity index (CCI). Patients were divided into 4 groups: CCI-none, CCI-low, CCI-moderate, and CCI-high. We calculated the relative risk (RR) of mortality within 90 days after surgery with a 95% confidence interval (CI), with stratification according to CCI group and year of surgery.

Results — 99,962 THAs and 63,718 TKAs were included. The proportion of THAs with comorbidity increased by 3–4% in CCI-low, CCI-moderate, and CCI-high patients, from 1996–1999 to 2010–2013. The overall 90-day mortality risk declined for both procedures. Compared to CCI-none, THA patients with low, moderate, and high comorbidity burdens had an RR of 90-day mortality of 1.9 (95% CI: 1.6–2.4), 1.9 (CI: 1.5–2.5), and 3.3 (CI: 2.6–4.2), respectively. Similar increases in proportions and RRs were observed in TKAs.

Interpretation — Despite the fact that the proportion of THA and TKA patients with comorbidities has increased over the past 18 years, the overall mortality has declined. The mortality risk depended on the comorbidity burden and did not decline during the study period for THA and TKA patients with a moderate or high comorbidity burden at the time of surgery.

The incidences of total hip arthroplasty (THA) and total knee arthroplasty (TKA) have increased worldwide over the last 2–3 decades (Pedersen et al. 2005, Singh 2011). From 1996 to 2013 in Denmark, the incidence of THA increased from 105 to 191 per 100,000 people. For TKA, the incidence increased from 30 to 167 per 100,000 people from 1997 to 2013 (Danish Hip Arthroplasty Register, Danish Knee Arthroplasty Register, Statistics Denmark). This increase in incidence may be explained not only by the aging of the population but also by the improved safety of the procedures, which has expanded the indications for surgery. Studies in the United States have shown that the proportions of THA and TKA patients with 1 or more comorbid conditions at the time of surgery have increased (Cram et al. 2011, Kirksey et al. 2012, Singh and Lewallen 2014).

Concurrent with the increased incidence of THA and TKA and the increasing proportion of patients with comorbid conditions, the mortality following both THA and TKA has decreased in several countries (Cram et al. 2011, Hunt et al. 2013, 2014). In a Danish study, Pedersen et al. (2014) found that the overall risk of all-cause mortality after THA and TKA decreased from 1% in 1997 to 0.6% in 2011. This may have been due to the introduction of enhanced recovery programs involving minimally invasive surgery, multimodal postoperative pain management, and early mobilization—all of which affect morbidity after THA and TKA (Andersen and Kehlet 2014, Glassou et al. 2014, Pedersen et al. 2014).

A few studies have explored the association between comorbidity and mortality in THA and TKA patients (Mahomed et al. 2003, Pedersen et al. 2011, Kirksey et al. 2012). However, changes in comorbidity burden over time and the effect of these changes on mortality following THA and TKA have not

yet been examined in population-based settings. The Danish medical registries and administrative databases together with each citizen's personal identification number permitted us to test our hypothesis that a decline in mortality risk would affect all patients regardless of comorbidity burden. We therefore examined changes in comorbidity burden and the impact on mortality over an 18-year period (1996 to 2013) in Danish patients who underwent primary THA and TKA due to osteoarthritis.

Patients and methods

The Danish Hip and Knee Arthroplasty Registers (DHR and DKR) were established in 1995 and 1997, respectively, and contain information about all primary THA and TKA procedures performed in Danish public or private hospitals. We used the personal identification number, which is unique to each resident and encoded in all Danish registries, to link primary procedures from the DHR and the DKR to the Danish National Patient Register (DNPR) and the Danish Civil Registration System (CRS). The DNPR contains data on all hospital admissions since 1977 and on all hospital outpatient and emergency room visits since 1995, including the dates of admission and discharge and up to 20 discharge diagnoses, recorded according to the International Statistical Classification of Diseases and Related Health Problems, Eighth Revision (ICD-8) until 1993 and Tenth Revision (ICD-10) thereafter (Schmidt et al. 2015). The CRS contains vital statistics on all Danish citizens (Schmidt et al. 2014).

Study population

We included all primary THAs registered in the DHR between January 1, 1996 and December 31, 2013, and all primary TKAs registered in the DKR between January 1, 1997 and September 30, 2013, due to primary osteoarthritis (100,399 THAs; 64,191 TKAs). Arthroplasties with either missing follow-up due to immigration (300 THAs; 399 TKAs) or personal identification number errors (128 THAs; 73 TKAs) were excluded. Arthroplasties with missing vital status as of March 31, 2014 (9 THAs) or December 31, 2013 (1 TKA) were also excluded. As the procedures were the object of interest, patients could be included twice for each type of arthroplasty. Altogether, 99,962 THA procedures and 63,718 TKA procedures were included in the study (Table 1).

Exposure: comorbidity

Comorbidity was established with the Charlson comorbidity index (CCI), which was originally developed to predict mortality. However, the CCI is commonly used to assess comorbidity in orthopedic patients due to its good prognostic value in terms of revision surgery, mortality, and various medical complications (Johnsen et al. 2006, Bjorgul et al. 2010, Pedersen et al. 2011, 2014). All 19 diagnoses recorded according

to the ICD-10 have been validated in a Danish context (Thygesen et al. 2011). The disease categories and related ICD-8 and ICD-10 codes are shown in Appendix 1 (see Supplementary data).

The CCI calculation was based on all primary and secondary diagnoses from hospitalizations and outpatient visits registered in the DNPR over a ten-year period before the primary procedure. The CCI score was calculated by adding the points of each disease category for each procedure. All THA and TKA procedures were then divided into 4 comorbidity burden groups based on the score (CCI-none = no comorbid conditions; CCI-low = comorbid conditions equal score 1; CCI-moderate = comorbid conditions equal score 2; and CCI-high = comorbid conditions equal score 3 or higher). Furthermore, we classified the THA and TKA procedures according to 4 specific disease groups nested in the CCI: diabetes (type-I and type-II diabetes, and diabetes with end-stage organ damage); cardiovascular diseases (myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease); cancer (any tumor, leukemia, lymphoma, or metastatic solid tumor); and chronic pulmonary disease (CPD).

Outcome: mortality

We obtained information on all-cause 90-day mortality from the CRS. The reason for looking at 90-day mortality was that this time frame reflects both risks in relation to surgery and the condition of the patient.

Statistics

All analyses were performed separately for THA and TKA. We described the study population according to age, sex, and comorbidity at the time of the primary procedure and also the type of fixation of the prosthesis and the length of hospital stay (LOS) in relation to the primary procedure. Age and LOS were expressed as medians and interquartile ranges (IQRs). LOS of more than 30 days was considered to be mainly a registration error and was recoded as 31 days (495 THAs (0.5%) and 445 TKAs (0.7%)). Information on LOS was missing in 4,107 THAs (4.1%) and 1,868 TKAs (2.9%).

The absolute risk of dying within 90 days of surgery was calculated as the percentage of individuals affected. We used Cox regression to estimate hazard ratios with 95% confidence intervals (CIs) as a measure of the relative risk (RR) of mortality according to year of surgery, using 1996/1997–1999 as the reference group. The proportionality was validated with log-log plots. Analyses were stratified according to comorbidity burden (CCI-none, CCI-low, CCI-moderate, and CCI-high). When looking at the 4 specific comorbid conditions, we used Cox regression to estimate hazard ratios (with CI) as a measure of the RR of mortality using those patients without the comorbid condition as the reference. A Cox regression estimating the RR of mortality according to CCI groups using the CCI-none as the reference group is presented in Appendix 2 (see Supplementary data).

Table 1. Number of procedures and characteristics of study population according to comorbidity burden measured with the Charlson comorbidity index (CCI), for total hip arthroplasty (THA) and total knee arthroplasty (TKA) patients. The CCI groups correspond to the following: CCI-none = no comorbid conditions; CCI-low = comorbid conditions equal score 1; CCI-moderate = comorbid conditions equal score 2; and CCI-high = comorbid conditions equal score 3 or higher

	CCI-none	CCI-low	CCI-moderate	CCI-high	Total (N)
THA					
No. of THAs, n (%)	69,292 (69)	15,022 (15)	10,092 (10)	5,556 (5)	99,962
in 1996–1999	11,511 (77)	1,919 (13)	1,150 (8)	424 (3)	15,004
in 2000–2004	16,988 (71)	3,603 (15)	2,223 (9)	1,129 (5)	23,943
in 2005–2009	21,909 (68)	4,925 (15)	3,316 (10)	1,967 (6)	32,117
in 2010–2013	18,884 (65)	4,575 (16)	3,403 (12)	2,036 (7)	28,898
Female, n (%)	39,281 (57)	8,245 (55)	5,798 (57)	2,890 (52)	56,214
Age at primary procedure (IQR)	69 (62–75)	72 (65–78)	73 (66–78)	74 (67–79)	70 (63–76)
in 1996–1999	70 (62–76)	73 (66–78)	73 (67–78)	73 (68–78)	71 (63–80)
in 2000–2004	70 (62–76)	72 (65–78)	73 (67–79)	74 (67–79)	70 (63–77)
in 2005–2009	68 (61–75)	71 (64–77)	72 (66–78)	73 (67–79)	69 (62–76)
in 2010–2013	69 (62–75)	71 (65–77)	72 (67–78)	74 (67–79)	70 (64–76)
LOS (IQR)	6 (3–9)	6 (3–9)	5 (3–9)	6 (3–9)	6 (3–9)
in 1996–1999	11 (9–14)	12 (9–15)	12 (9–14)	13 (10–16)	11 (9–14)
in 2000–2004	7 (9–11)	9 (7–12)	9 (8–12)	10 (8–13)	9 (7–11)
in 2005–2009	4 (3–6)	5 (4–7)	5 (3–7)	5 (4–8)	5 (3–7)
in 2010–2013	3 (2–3)	3 (2–4)	3 (2–4)	3 (2–5)	3 (2–4)
Fixation, %					
cemented	30	33	34	34	31
uncemented	48	45	43	44	47
hybrids	22	22	23	22	22
TKA					
No. of TKAs, n (%)	41,013 (64)	11,109 (17)	7,256 (11)	4,340 (7)	63,718
in 1996–1999	2,737 (73)	538 (14)	330 (9)	132 (3)	3,737
in 2000–2004	8,117 (67)	2,114 (17)	1,281 (10)	665 (5)	12,177
in 2005–2009	15,984 (64)	4,331 (17)	2,842 (11)	1,760 (7)	24,917
in 2010–2013	14,175 (62)	4,126 (18)	2,803 (12)	1,783 (8)	22,887
Female (%)	26,782 (65)	6,864 (62)	4,559 (63)	2,436 (56)	40,641
Age at primary procedure (IQR)	69 (62–76)	71 (64–77)	72 (66–78)	73 (66–78)	70 (63–76)
in 1996–1999	72 (64–77)	72 (66–78)	74 (67–79)	73 (65–78)	72 (65–78)
in 2000–2004	70 (63–77)	71 (64–77)	74 (67–79)	74 (68–79)	71 (64–77)
in 2005–2009	68 (62–75)	71 (64–77)	72 (66–78)	73 (66–79)	76 (63–76)
in 2010–2013	68 (62–75)	70 (64–76)	71 (65–77)	72 (66–77)	69 (63–76)
Median LOS (IQR)	5 (3–8)	5 (3–8)	5 (3–8)	5 (3–8)	5 (3–8)
in 1996–1999	14 (11–16)	14 (11–17)	14 (11–18)	13.5 (10–18)	14 (11–16)
in 2000–2004	10 (8–13)	10 (8–13)	10 (8–13)	11 (8–14)	10 (8–13)
in 2005–2009	5 (3–7)	5 (3–7)	5 (3–7)	6 (4–8)	5 (3–7)
in 2010–2013	3 (2–4)	3 (2–4)	3 (2–4)	3 (3–5)	3 (2–4)
Fixation, %					
cemented	76	78	78	77	76
uncemented	8	6	7	6	7
hybrids	16	16	15	17	17

IQR: interquartile range; LOS: length of stay.

Age at primary procedure and sex were considered to be confounders. Age was divided into 5 categorical groups: 10–49, 50–59, 60–69, 70–79, and 80+ years. The type of fixation (cemented, uncemented, and hybrid implants) was considered a potential confounder, but did not contribute to the regression models and was therefore omitted. Age, sex, and type of fixation were examined for interactions with the covariates before being entered into the model. No interactions were identified.

We included patients with multiple THAs and TKAs, acknowledging violation of independency. We performed a

sensitivity analysis including only the first THA or TKA (data not shown). The characteristics of the study population and the RR estimates in the sensitivity analyses did not diverge from the current estimates.

The analyses were performed using Stata statistical software release 12.0.

Ethics

Permission for the study was obtained from the Danish Data Protection Agency (reference number: 2012-41-0636).

Results

Patient characteristics (Table 1)

The median age at primary procedure was higher in the CCI-high group than in the CCI-none group, for both THA and TKA. The proportion of males increased with increasing comorbidity. This was most apparent for TKA, where 35% of the patients in the CCI-none group and 44% in the CCI-high group were males. The median LOS decreased from 11 (THA) and 14 (TKA) days in the early period (1996/1997–1999) to 3 days in the most recent period (2010–2013). The LOS declined during the study period irrespective of comorbidity group.

The proportion of patients with a comorbidity burden increased over time from the early period (1996/1997–1999) to the most recent period (2010–2013) (Table 1 and Figure 1). The increase was 3–4 percentage points in the 3 comorbidity groups, for both THA and TKA. Corresponding decreases were observed for THA and TKA without a comorbidity burden at the time of the primary procedure.

The proportions of the 4 specific comorbid conditions are shown in Table 2 (Supplementary data). The most common condition for both THA and TKA during the study period was cardiovascular disease. The proportion of patients with cardiovascular disease increased from 9% in 1996/1997–1999 to 14% in 2010–2013, in both THA and TKA. The proportions of patients with diabetes, cancer, and chronic pulmonary disease all increased over the study period. The largest increase was observed for diabetes. For THA, the proportions were 2.4% in 1996–1999 and 5.9% in 2010–2013. For TKA, the

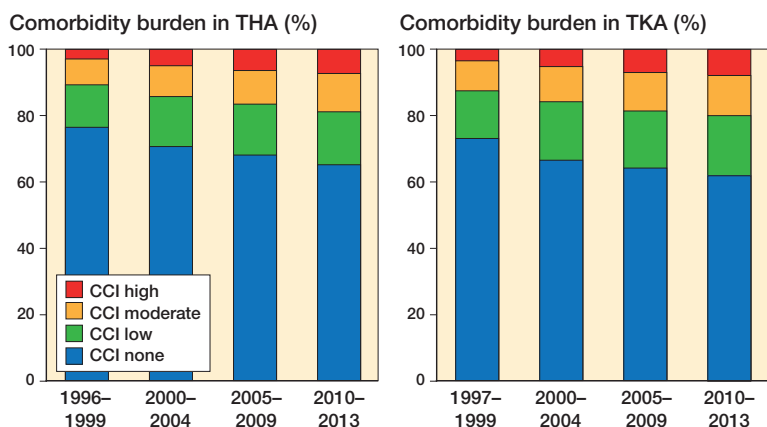


Figure 1. The distribution of total hip (left panel) and knee arthroplasty (right panel) procedures according to comorbidity burden.

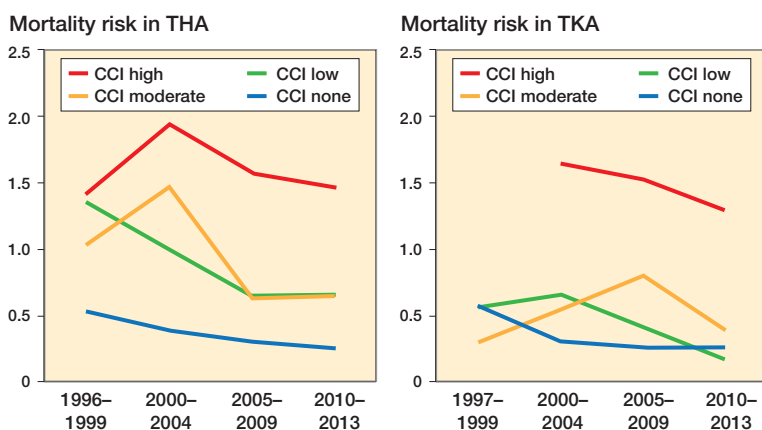


Figure 2. Development in risk of mortality in total hip (left panel) and knee arthroplasty (right panel) procedures according to comorbidity burden.

proportions were 3.6% in 1997–1999 and 8.9% in 2010–2013 (Table 2, see Supplementary data).

Overall mortality

During the total study period, for THA the 90-day absolute mortality risk declined from 0.70 (CI: 0.57–0.85) to 0.45 (CI: 0.38–0.54) and for TKA it declined from 0.54 (CI: 0.33–0.83) to 0.34 (CI: 0.27–0.43) (data not shown). In THA patients, the adjusted RR of mortality at 90 days post-surgery was 0.66 (0.51–0.85) in 2010–2013 compared to 1996–1999. In TKA patients, the adjusted RR of mortality at 90 days post-surgery was 0.68 (0.41–1.11) in 2010–2013 compared to 1997–1999 (Table 3, see Supplementary data).

The effect of comorbidity on mortality

For THA patients with no or low comorbidity burden, we observed reduced RRs of dying, from 2005–2009 and onward compared to the early time period (1996–1999). For TKA patients, there were reduced RRs only for patients with no comorbidity burden (Table 3, see Supplementary data).

There was increased mortality for THA patients in the CCI-low, CCI-moderate, and CCI-high groups in all time periods compared to the CCI-none group. For TKA patients, only the CCI-high group had an increased RR of dying within 90 days post-surgery, but the difference was found in all time periods (Figure 2 and Appendix 2, see Supplementary data).

For THA and TKA patients with diabetes or cardiovascular diseases at the time of the primary procedure, the RR of dying within 90 days post-surgery was higher than in patients without these diseases (Table 2, see Supplementary data). Cancer and CPD at the time of the primary procedure did not affect the RR of dying within 90 days post-surgery.

Over the entire study period, we found an increased RR of dying within 90 days of surgery, with increasing comorbidity burden for both THA and TKA patients—but this was not statistically significant for TKA patients in the CCI-low group (Appendix 2, Supplementary data).

Discussion

This study shows that the number of THA and TKA procedures performed on patients with comorbidities has increased over the past 18 years. In addition, the overall mortality risk at 90 days post-surgery declined for both procedures. The mortality risk depended on the comorbidity burden. During the study period, the 90-day mortality risk did not decline for THA and TKA patients with a moderate or high comorbidity burden at the time of surgery.

Patient characteristics

Despite the differences in populations and settings, our finding of an increasing comorbidity burden corresponds to findings from large American cohort studies (Cram et al. 2011, Kirksey et al. 2012, Singh and Lewallen 2014). For THA, Kirksey et al. (2012) found that the comorbidity burden measured with the Deyo comorbidity index increased by 30%, and for TKA by 35%, from 1998 to 2008. Singh and Lewallen (2014) found that the mean comorbidity score in THA patients, measured with the Deyo-Charlson comorbidity index, increased from 0.9 in 1993–1995 to 1.1 in 2002–2005, and the proportion of THA patients with a Deyo-Charlson score of 3 or more increased from 12% to 15% during the same period. This finding differs somewhat from ours. We observed a larger increase but from a much lower starting point, with the proportion of THA patients in the CCI-high group increasing from 2.8% in 1996–1999 to 7.1% in 2010–2013. Different populations, settings, and comorbidity indices might explain some of the difference. However, another likely explanation is the difference in how comorbidity is determined. We used prospectively reg-

istered diagnoses from hospitalizations and outpatient visits over a 10-year period before the primary procedure, and the fact that we concentrated more on registration of comorbidity diagnoses during the study period might explain some of the large increase in comorbidity in our study.

The prevalence of diabetes in THA patients in the study by Singh and Lewallen (2014) increased from 4.8 in 1993–1995 to 8.0 in 2002–2005. Cram et al. (2011) used the Elixhauser comorbidity index to evaluate approximately 1.5 million Medicare THA patients, and found that the mean number of comorbid conditions increased from 1 to 2 and that the prevalence of diabetes increased from 7.1% to 15.5% over an 18-year period (1991–2008). The prevalence of diabetes in our study was comparable to that in the study by Singh and Lewallen, but was less than that observed by Cram et al. (2011). Discrepancies in how diabetes is defined and the fact that our study population, similar to that of Singh and Lewallen, included patients younger than 65 years of age at the time of the primary procedure may explain the difference.

The effect of comorbidity on mortality

The overall risk of mortality across comorbidity groups declined between 1996/97 and 2013, in accordance with earlier findings (Cram et al. 2011, Hunt et al. 2013, 2014, Pedersen et al. 2014). The decline in mortality risk was, however, dependent on patient comorbidity burden. This was opposite to what we expected. Due to the introduction of enhanced recovery programs, we expected the effect of the comorbidity burden to have been less important over the 18 years of interest. The prognosis was best for patients without comorbid conditions at the time of the primary procedure, and the risk of mortality decreased during the study period in this group of patients. For patients with a comorbidity burden at the time of surgery, the mortality risk was mainly unchanged during the study period. In addition, for patients with comorbid conditions, we found an increasing mortality risk with increasing comorbidity burden over the entire study period. Enhanced recovery programs were widely introduced in Denmark during the study period (Glassou et al. 2014), and they may be an important factor in the overall reduction in mortality after THA and TKA. We found a reduction in LOS in all comorbidity groups during the study period, reflecting this change, but surprisingly patients with severe comorbidity did not benefit from the reduction in mortality risk after THA and TKA with the introduction of enhanced recovery programs. Similar results were found in the study by Kirksey et al. (2012). Despite an overall decrease in in-hospital mortality, these authors found that a higher Deyo index score increased the risk of in-hospital mortality after both THA and TKA.

We found that THA and TKA patients with diabetes and cardiovascular diseases prior to the primary procedure had an increased risk of dying. Several studies support these findings (Bozic et al. 2012a, b, Hunt et al. 2013, Jämsen et al. 2013, Hunt et al. 2014, Belmont et al. 2014a, b). Bozic et al. (2012 a,

b) found that congestive heart failure, metastatic cancer, renal disease, cerebrovascular disease, and chronic pulmonary disease—all of which were included in the CCI—increased the 90-day postoperative mortality risk after THA and TKA. In 2 large British cohort studies looking at short-term mortality in THA and TKA patients, Hunt et al. (2013, 2014) found that congestive heart failure, myocardial infarction, cerebrovascular disease, moderate/severe liver disease, and renal disease were associated with increased mortality within 45 days of TKA or within 90 days of THA.

Strengths and limitations

The CCI was originally developed to quantify the influence of comorbidity on survival and is also widely used in orthopedic research (Johnsen et al. 2006, Bjorgul et al. 2010, Pedersen et al. 2011, 2014, Glassou et al. 2014). However, the use of the CCI has some limitations. Although registration in the DNPR is compulsory and reimbursement-related, some diagnoses may have been under-reported. Due to the absence of data from outpatient visits from before 1995, due to changes in coding practice and diagnosis criteria, and because the CCI does not capture diseases treated only by GP, we may have underestimated some mild cases of e.g. CPD, diabetes, or cardiovascular diseases—especially in the early time periods, leading to an underestimation of the risk. Missing information on comorbid conditions that were not included in the CCI calculation but that still contributed to an early death, such as psychiatric conditions, may also have affected the findings. The use of other comorbidity instruments, such as the Elixhauser comorbidity index, which includes 30 comorbid conditions, could have addressed this problem. However, the CCI is the preferred instrument when assessing preoperative health status in the 2 Danish joint registries (Danish Hip Arthroplasty Register, Danish Knee Arthroplasty Register).

The major strengths of our study were the size and the use of valid public medical registries and administrative databases. The completeness of registration data for primary THA and TKA in the DHR and DKR is more than 95% (Pedersen et al. 2004, 2012, Danish Hip Arthroplasty Register, Danish Knee Arthroplasty Register). In addition, given the public healthcare system in Denmark, we examined patient characteristics in an unselected population. Despite the advantages of this design, our results depend on the validity of the exposure, as mentioned above. Mortality was selected as the outcome of interest because the Danish personal identification number system makes it impossible to under-report mortality, as could be the case with other adverse events, but other clinical adverse events and patient-reported outcomes would also be of importance. Several studies have shown that obesity may be of importance in relation to postoperative adverse events (Bozic et al. 2012b, Singh and Lewallen 2014, Belmont, Jr. et al. 2014a, b, Alvi et al. 2015). Unfortunately, information about BMI is not available in the joint registries or the administrative databases. However, there is reason to believe that

concomitant medical conditions related to obesity are covered by the diagnoses in the CCI. Therefore, the missing information on obesity may not be of importance to our findings.

The proportion of OA patients with comorbidities who underwent THA or TKA increased from 1996 to 2013. At the same time, the overall mortality risk within 90 days of the primary THA or TKA procedure declined. However, the mortality risk was dependent on the comorbidity burden. While the mortality declined during the study period for patients with no or low comorbidity burden at the time of the primary procedure, the 90-day mortality risk did not decline during the study period for THA and TKA patients with a moderate or high comorbidity burden. Information concerning increased mortality rates in patients with multiple or severe comorbid conditions is of importance for both patient and surgeon when counseling this expanding group of patients.

Supplementary data

Tables 2 and 3 and Appendices 1 and 2 are available in the online version of this article.

All the authors contributed to the conception of the study, to the study design, and to the discussion and interpretation of the results. ENG drafted the article. ABP and TBH revised the manuscript for intellectual content and approved the final version before submission.

No competing interests declared.

Danish Hip Arthroplasty Register 2015. Online Source, <http://www.dhr.dk>

Danish Knee Arthroplasty Register 2015. Online Source, <http://www.kea.au.dk/da/kliniskvalitet/kliniske-databaser/KnaealoplastikRegister.html>

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