Multimorbidity measured with Charlson Comorbidity Index is not associated with clinically relevant risk of revision after primary total hip arthroplasty: a population-based cohort study on 98,647 patients from the Danish Hip Arthroplasty Register

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Background and purpose — Evidence for guiding healthcare professionals on the risks of total hip arthroplasty (THA) in multimorbid patients is sparse. We aimed to examine the association between multimorbidity and the risk of revision due to any cause and specific causes after primary THA due to osteoarthritis.

Patients and methods — We identified 98,647 THA patients and subsequent revisions in the Danish Hip Arthroplasty Register from 1995 to 2018. Multimorbidity was measured with the Charlson Comorbidity Index (CCI). Using the CCI (low, medium, high), we calculated the cumulative incidence function (CIF) of first revision up to 10 years after THA. Adjusted cause-specific hazard ratios (aHRs) were estimated using Cox regressions. All estimates are presented with 95% confidence intervals (CI).

Results — Overall, the prevalence of patients with low, medium, and high CCI was 70%, 24%, and 6%. The CIF of any revision within 10 years was 6.5% (CI 6.2–6.7) in low and 6.5% (CI 5.8–7.3) in high CCI, with an aHR of 1.4 (CI 1.2–1.6) for patients with high compared with low CCI. The corresponding aHRs for cause-specific revision were 1.3 (CI 1.0–1.6) for aseptic loosening within 10 years, 1.2 (CI 0.9–1.6) for infection, and 1.7 (CI 1.3–2.2) for dislocation, both within 2 years.

Conclusion — Multimorbidity is associated with a minor but not clinically relevant increased risk of revision up to 10 years after primary THA.

Total hip arthroplasty (THA) is said to be a successful and safe procedure but is associated with revisions due to infection and dislocation that typically occur within the first years after THA, whereas revision due to aseptic loosening occurs several years after THA. Previous research has identified numerous patient- and surgery-related factors for revision surgery, but multimorbidity has been given little attention.

Multimorbidity is defined as the coexistence of 2 or more chronic conditions in the same individual [1]. Due to different methods of measuring multimorbidity [2] the prevalence reported differs greatly, ranging from 13% to 73% [3]. Based on hospital contacts, the prevalence of multimorbidity was 25% in Denmark for patients who underwent THA due to osteoarthritis (OA) in 2018 [4]. In contrast, based on prescription data, a prevalence of 80% in 2018 was reported in Australia [5].

Previous studies examining the association between multimorbidity and risk of revision surgery [5-7] are hampered by several methodological problems including non-uniform definition of multimorbidity and differences in statistical methods used. Thus, evidence for guiding healthcare professionals on the risks of THA in patients with multimorbidity remains partly unclear, especially from countries with free access to healthcare for all residents. Therefore, we conducted a population-based cohort study to examine the association between multimorbidity and cumulative incidence and risk of revision due to any cause and specific causes after primary THA due to OA.

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Patients and methods

Study design and population

The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Using the Danish Hip Arthroplasty Register (DHR), we conducted a study on prospectively collected data from 98,647 patients undergoing primary THA due to OA from January 1, 1995 to December 31, 2018. The DHR is a Danish national quality database, which includes both primary THA and revisions. The DHR was established in 1995 and all public orthopedic departments and private hospitals in Denmark performing these surgeries report to the DHR. The registration completeness for primary THAs is ~95%, whereas the registration completeness for revisions is ~90% [8], being stable during the last decade. Only the first THA due to OA performed on the patient was included.

The study population was linked to the Danish National Patient Registry (DNPR), Statistics Denmark, and the Civil Registration System (CRS) by the unique 10-digit personal identification number given to all Danes at birth or immigration since 1968. All Danish medical registries encode this number, which allows individual-level linkage of data between multiple registries [9]. The CRS also contains information on date of birth, age, sex, cohabitation, and vital status [9].

Multimorbidity

With a primary focus on the burden of somatic diseases, the Charlson Comorbidity Index (CCI) [10] was chosen as a proxy for multimorbidity. To compute CCI, we used ICD-8 or ICD-10 codes registered in the DNPR [11], which contains all non-psychiatric hospital admissions since 1977 along with clinical and emergency visits since 1995 [11]. The 8th revision was used for coding until 1994 and the 10th revision thereafter [11] (Table 8, see Supplementary data). Based on the weighted CCI score (range 0–37 points), patients were categorized into low (0 points), medium (1–2 points), and high (≥ 3 points) multimorbidity burden [10,12]. The lookback period for diagnosis was 10 years prior to the primary THA.

Revision

The primary outcome was first-time revision due to any cause (any revision), whereas secondary outcomes were revisions due to the specific causes of aseptic loosening, infection, and dislocation. Revisions were identified in the DHR including any surgery to exchange or remove parts of or the entire hip prosthesis.

Covariates (Table 1)

The following variables were included in the dataset and collected at the time of primary THA:

Table 1. Characteristics of patients undergoing primary total hip arthroplasty (THA) due to osteoarthritis (OA) in the pe-riod 1995–2018 in Denmark. Values are count (%) unless otherwise specified

Factor	CCI low	CCI medium	CCI high
Total	69,229 (70)	23,948 (24)	5,470 (6)
Female sex	39,172 (57)	13,234 (55)	2,787 (51)
Median age (IQR)	68 (61–74)	72 (66–77)	74 (68–79)
< 60	14,627 (21)	2,498 (11)	355 (6)
60–70	24,864 (36)	7,478 (31)	1,460 (27)
70–80	23,996 (35)	10,532 (44)	2,603 (48)
≥ 80	5,742 (8)	3,440 (14)	1,052 (19)
Cohabiting status			
Living alone	22,005 (32)	8,833 (37)	2,176 (40)
Cohabiting	47,224 (68)	15,115 (63)	3,294 (60)
Highest obtained educational level			
Low	29,471 (42)	11,236 (47)	2,627 (48)
Medium	27,508 (40)	9,100 (38)	2,100 (38)
High	12,250 (18)	3,612 (15)	743 (14)
BMI [a], total n	9,223	3,761	1,061
< 18.5	98 (1)	35 (1)	11 (1)
18.5–24.9	3,053 (33)	1,173 (31)	303 (29)
25.0–29.9	3,775 (41)	1,502 (40)	433 (41)
≥ 30	2,297 (25)	1,051 (28)	313 (29)
Fixation method			
Cemented	15,471 (22)	6,028 (25)	1,393 (25)
Uncemented	39,597 (57)	12,464 (52)	2,738 (50)
Hybrid	13,775 (20)	5,302 (22)	1,287 (24)
Other [b]	386 (1)	154 (1)	52 (1)
Surgery year			
1995–2000	10,547 (15)	2,544 (11)	312 (6)
2001–2006	15,827 (23)	5,081 (21)	1,034 (19)
2007–2012	20,473 (30)	7,442 (31)	1,718 (31)
2013–2018	22,382 (32)	8,881 (37)	2,406 (44)

IQR: interquartile range. BMI: body mass index.
[a] Only available from 2016–2018.
[b] Other refers to fixation other than cemented, uncemented, hybrid A or B, registered by the surgeon in the Danish Hip Arthroplasty Register.

- Patient sex, age, and cohabiting status (categorized into alone, cohabiting, or missing) were derived from the CRS [9].
- Highest obtained educational level (categorized as low, medium, high, or missing) were retrieved from the Integrated Database for Labor Market Research at Statistics Denmark [13]. Low educational level was defined as primary education or lower secondary education. Vocational Education and Training (VET), qualifying educational programs, upper secondary education, and short cycle tertiary were categorized as medium educational level. Bachelor's programs, master's programs, and Ph.D. programs were defined as high educational level. Not stated educational level was considered a missing value.
- Surgery year (in categories, 1995–2000, 2001–2006, 2007–2012, 2013–2018), fixation method of the prosthesis (cemented, uncemented, hybrid, or other), and body mass index (BMI) (categorized according to World Health Organization (WHO) < 18.5, 18.5–24.9, 25–29.9) were retrieved from the DHR.

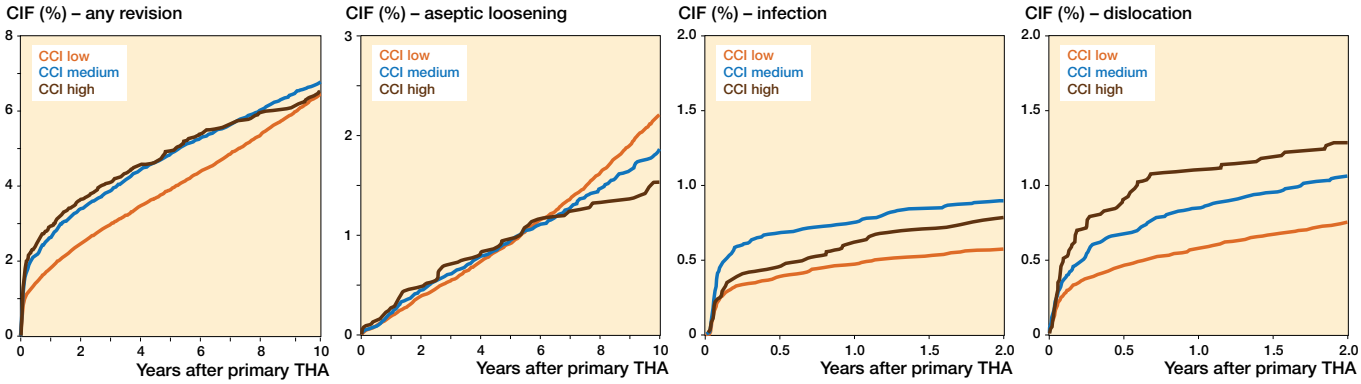

Figure 1. Cumulative incidence function (CIF) plots providing crude risk of any first-time revision surgery due to aseptic loosening, infection, and dislocation after primary total hip arthroplasty (THA) due to osteoarthritis for the three multimorbidity groups measured with Charlson Comorbidity Index (CCI).

Statistics

The baseline characteristics of the study population were described using descriptive statistics. Age and follow-up time are presented with median and interquartile range (IQR) (Table 1). For the patients excluded due to missing values on cohabitation or education, a missing-data analysis of the patient characteristics was conducted. Patients were followed from the date of primary THA to the first revision surgery, emigration, death, or end of follow-up, whichever came first. To provide a clinical perspective, crude risk of revision from cumulative incidence functions (CIF) with 95% confidence intervals (CI) of the first-time revision due to any cause was calculated using the Aalen–Johansen method [14], thereby treating death as a competing risk (Figure 1). To provide a surgeon's perspective, net risk of revision calculated by the Kaplan–Meier method was also conducted (Figure 2, see Appendix). Cause-specific CIFs for the 3 specific causes of revision surgery with death and all other revision causes as competing risks were also calculated. These plots were likewise censored according to the time the outcomes typically occur after primary THA and complying with legislation rules. Thus, all analyses were censored at 10 years due to Danish statutory privacy restrictions. All outcomes were evaluated by 0–2 years. Any revision and aseptic loosening were also evaluated within 0–5 and 0–10 years after primary THA. Each outcome was analyzed by a separate Cox proportional regression model for each time interval to estimate cause-specific hazard ratios (HR) with CI. A directive acyclic graph (DAG) was drawn to decide which covariates were relevant to include as potential confounders. Multimorbidity is closely related to socioeconomic status, which is also known to be associated with revision risk [15]. Thus, the HRs were adjusted for age, sex, surgery year, and social factors such as educational level and cohabitation status. However, the absolute measures remain unadjusted for this association. The assumption of proportional rates was controlled graphically by assessing log–log plots and observed versus expected survival curves.

Due to the long follow-up period with shifting hospital and operational procedures from 1995 to 2018, CIFs stratified on surgery year were calculated to eliminate potential informative censoring. Analyses stratified on sex, age, surgery year, fixation method, and cohabitation status were conducted to investigate interactions. The Cox regression estimates are supplemented with forest plots, numbers of events, and analysis time (person-years). All analyses were performed using the statistical software STATABE17 (StataCorp, College Station, TX, USA).

Ethics, funding, and disclosures

According to Danish law, ethics committee approval is not required for registry-based studies. The study was reported to the Danish Data Protection Agency through registration at Aarhus University (record number: AU-2016-051-000001, sequential number 880). The study was supported by the Danish foundation for orthopaedic research. The authors report no conflict of interest. Complete disclosure of interest forms according to ICMJE are available on the article page, doi: 10.2340/17453674.2024.35225

Results

Study population demographics

113,995 patients with one THA procedure due to OA were identified. 15,348 patients were excluded due to missing data on cohabitation status or education level, leaving 98,647 patients with complete data in the final study population (Figure 3). About 58% of patients in CCI medium had a score of 1, whereas 87% in CCI high had a score from 3–5 (ranging from 3 to between 10 and 15) (Table 2, see Appendix).

Compared with patients with CCI low, patients with CCI high were older (median age 74 years vs. 68 years), and less often operated on at the beginning of the study period (6% vs. 15% in 1995–2000) (Table 1). The distribution of deaths before any first revision within 10 years was unequally distributed between CCI high vs. low (35% vs. 12%) (Table 3, see Appendix).

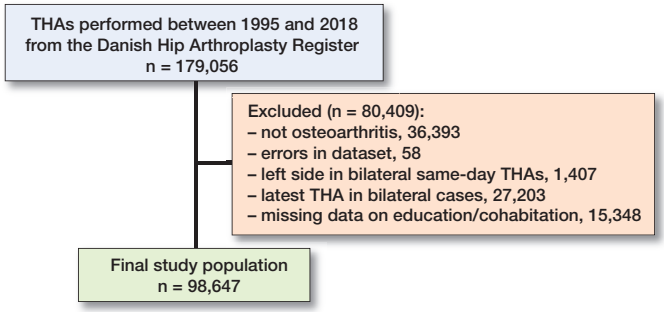

Figure 3. Flowchart of the study population undergoing primary total hip arthroplasty (THA) due to osteoarthritis (OA) in Denmark from 1995–2018.

Table 4. Cumulative incidence function estimates with 95% confidence intervals (CI) in percentages (%) from Aalen–Johansen analyses for any first-time revision and due to aseptic loosening, infection, and dislocation divided into the 3 exposure groups measured with Charlson Comorbidity Index (CCI)

Factor	CCI low	CCI medium	CCI high
0–2 years			
Any revision	2.5 (2.3–2.6)	3.4 (3.2–3.6)	3.6 (3.2–4.2)
Aseptic loosening	0.4 (0.3–0.4)	0.5 (0.4–0.5)	0.5 (0.3–0.7)
Infection	0.6 (0.5–0.6)	0.9 (0.8–1.0)	0.8 (0.6–1.1)
Dislocation	0.8 (0.7–0.8)	1.1 (1.0–1.2)	1.3 (1.0–1.6)
0–5 years			
Any revision	3.9 (3.8–4.1)	4.9 (4.6–5.2)	4.9 (4.3–5.6)
Aseptic loosening	0.9 (0.8–1.0)	1.0 (0.8–1.1)	1.0 (0.7–1.3)
0–10 years			
Any revision	6.5 (6.2–6.7)	6.8 (6.4–7.2)	6.5 (5.8–7.3)
Aseptic loosening	2.2 (2.1–2.4)	1.9 (1.7–2.1)	1.5 (1.2–2.0)

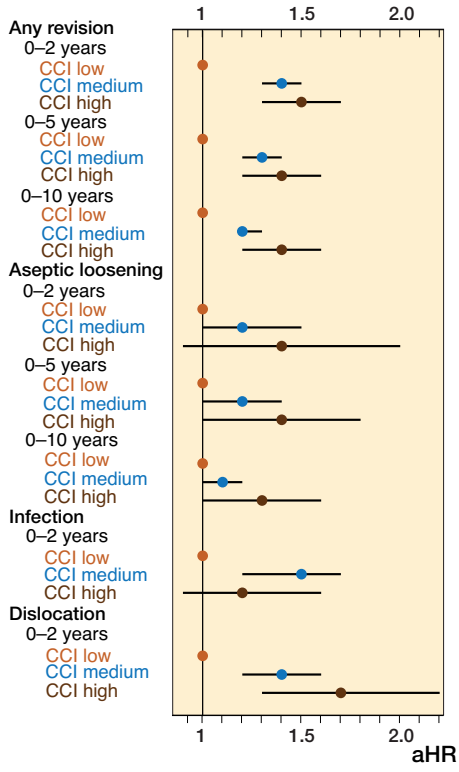

Figure 4. Forest plot and adjusted cause-specific hazard ratios (aHRs) for first-time revision after primary total hip arthroplasty (THA) due to osteoarthritis (OA) in patients receiving a THA in the period 1995–2018 using CCI low as reference. aHR: cause-specific hazard ratio adjusted for age, sex, surgery year, and social factors such as educational level and cohabitation status. CI = 95% confidence interval. Measure of multimorbidity: CCI low = patients with score of 0 on Charlson Comorbidity Index (CCI) when receiving THA, CCI medium = patients scoring 1 or 2 on CCI, and CCI high = patients scoring ≥ 3 on CCI.

Multimorbidity and revision

The crude risk of any revision was similar among the 3 multimorbidity groups at 10 years' follow-up at 6.5% (CI 6.2–6.7) for CCI low, 6.8% (CI 6.4–7.2) for CCI medium, and 6.5% (CI 5.8–7.3) for CCI high (Table 4). The 10-year crude risk of revision due to aseptic loosening and 2-year crude risk of revision due to infection were also similar among the groups but a with little higher risk for revisions due to dislocation (Table 4). With CCI low as a reference, the cause-specific aHR was increased for CCI medium and CCI high for any revision and aseptic loosening within 10 years and for infection and dislocation within 2 years (Figure 4 and Table 5, see Appendix). All relative estimates point towards multimorbidity being associated with an increased revision rate (Figure 4). The stratified CIF curves did not provide any indication of informative censoring. Therefore, 1 CIF plot was presented for each outcome. The results of the stratified analyses using Cox regression on sex, age, cohabitation, and surgery year were not considered clinically significantly different from the main analysis. When stratifying on cemented and uncemented fixation, the tendency in the association between multimorbidity and revision was consistent for any revision at all timepoints and for infection and dislocation. For aseptic loosening, we found slightly different strengths of the association between multimorbidity and revision. For uncemented, the association increased for CCI medium but vanished for CCI high. For cemented, the association increased for CCI high and decreased slightly for CCI medium.

For number of patients with specified diseases in CCI medium and high and number of patients at risk, see Tables 6 and 7 in Supplementary data.

Discussion

We aimed to examine the association between multimorbidity and the risk of revision due to any cause and specific causes after primary THA due to OA. We found a similar cumulative incidence of revisions among CCI groups. There was a slightly increased relative risk of any revision and revisions due to specific causes up to 10 years after primary THA for patients in CCI high compared with CCI low. However, the crude differences in revision risk between the 3 multimorbidity groups are considered small without clinical significance.

Multimorbidity is associated with high utilization of healthcare [16], which means that multimorbid patients must cope with many treatments in a specialized healthcare system. Their medical state, use of medications, and age are also likely to affect healing and bone density, which are relevant factors when choosing the fixation method that is associated with different revision risks [17]. This could also explain the variance in the association identified in the stratified analyses on fixation method as the clinical decision-making at the primary THA done by the surgeon affects the results of these analyses.

The similar crude revision risk in the 3 CCI groups might be explained by high mortality in the CCI high group during the follow-up. Part of the population who are multimorbid are likely dead within the first years after primary THA and thus not alive to experience the event occurring over a longer time. This was the case for this study, where a higher number of deaths were present for CCI high (Table 3, see Appendix). Comparing the crude and net risk of revision, no large difference in the absolute risk is present (Figure 2, see Appendix). However, the curves of any revision and aseptic loosening no longer drop for CCI high, indicating that deaths influence the association.

Comparison with other studies

Other studies investigating the association between multimorbidity and revision in THA patients have used slightly different multimorbidity indices or methods to measure the burden, had different study periods, revision outcomes, and statistical methods including handling confounding. Despite this, our results are consistent with previous studies pointing to multimorbidity as a risk factor for revision surgery. A Swedish and Genevan study also found small absolute differences between multimorbidity groups within 5 years' follow-up using ASA score as exposure along with an increased HR with higher ASA scores [18]. In a Finnish study with a simple count of diseases, the occurrence of 1 or more of the included diseases (analyzed with Cox regression) was associated with slightly increased revision rate. The same tendency was seen in a Spanish study (using the Elixhauser Comorbidity Index) [7]. An Australian predictive study found using the Elixhauser index that the OR was 1.7 (CI 1.3–2.2) when comparing a score of ≥ 3 with a score of 0. Using a third pharmacy-based comorbidity measure (RxRisk-V), the OR was ≥ 1.5 for all categories higher than 2 points compared with a score of 0 [5]. Our study, with a 10-year follow-up period that also presents the specific revision causes as secondary analyses on a nationwide cohort of patients with OA, adds a more thorough description and thereby provides relevant knowledge when considering the primary surgery.

Strength

First, we included death as a competing risk when having an elderly study population, multimorbidity as exposure, and an outcome that has severe consequences for the patient [19]. Second, the combination of both cause-specific HR and CIFs gives a better foundation for clinical decision-making. Third, all the data was retrieved from nationwide registries, allowing the combining variables to handle confounding and complete follow-up of all patients. Fourth, CCI includes the most common somatic diseases, which are likely to correlate with the surgeon's clinical decision-making.

Limitations

First, some misclassifications of CCI are possible. CCI is based only on hospital contacts and thus captures only severe conditions requiring hospitalization. Less severe conditions treated by the general practitioner are not captured. Generally, the registration of comorbidities has increased over time, potentially leading to underestimation of the exposure for the earliest years due to the 10-year lookback period. Second, patients with a CCI score of 0 are considered as having a low burden instead of none, because of these limitations in the calculation of CCI. The misclassification of CCI is unlikely to be related to revision surgery as an outcome, thus our estimates will at most be biased towards the null.

Third, not all infections are captured in DHR. Revision due to infection has a sensitivity of 67% and a positive predictive value (PPV) of 77% [20]. In Denmark, the surgeon registers into the DHR immediately after surgery, where microbiology answers are not yet available. Therefore, some infections could be misclassified. This would result in an underestimation of infection as the cause of revision. Fourth, misclassification may also explain the relatively high number of aseptic loosenings in the first years after primary THA. The validity of aseptic loosening and dislocation are not known. However, the misclassification is unlikely dependent on CCI.

Fifth, a study from the UK found that up to 2/3 of the patients with multimorbidity might not undergo the primary THA [21]. Therefore, our study population might be selected by including only the "most healthy" patients with multimorbidity. This will also add to the explanation of relatively few revisions in patients with high CCI due to an initial risk evaluation excluding them from the primary THA.

Sixth, we did not adjust for BMI due to unavailability of data for the entire study population, thus unmeasured confounding from BMI is possible [7].

Conclusion

We found similar cumulative incidence of revisions among CCI groups. There was a slightly increased relative risk of any revision and revisions due to specific causes up to 10 years after primary THA for patients in CCI high compared with CCI low. However, the crude differences in revision risk between the 3 multimorbidity groups are considered small and without clinical significance.

Supplementary data

Tables 6–8 are available as Supplementary data on the article page, doi: 10.2340/17453674.2024.35225

RSH performed all statistical analyses and drafted the manuscript. All authors have contributed to the conception and design of the study, critical analyses of the data, interpretation of the findings, and critical revision of the manuscript through all stages of the study.

Handling co-editors: Keijo Mäkelä and Philippe Wagner
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Appendix

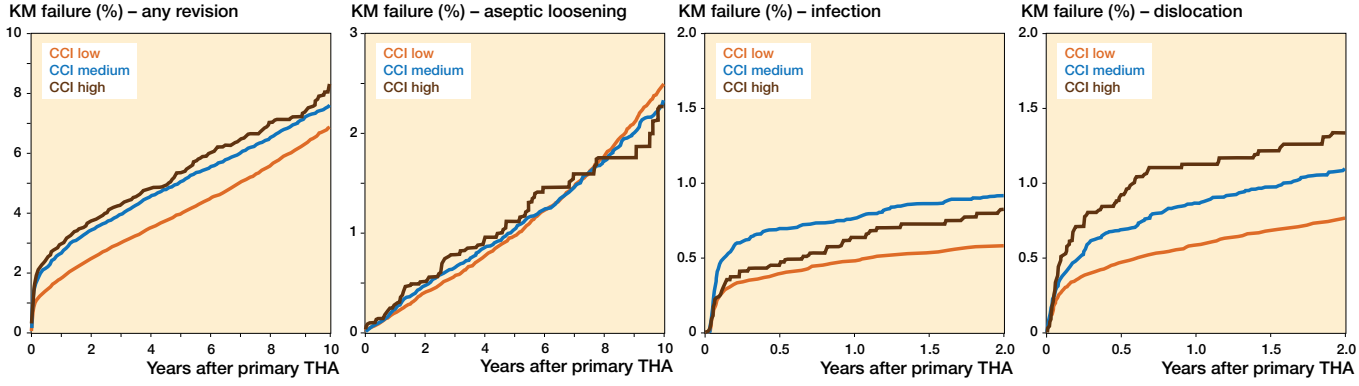

Figure 2. Kaplan–Meier curves providing net risk of any first-time revision surgery due to aseptic loosening, infection, and dislocation after primary total hip arthroplasty (THA) due to osteoarthritis for the 3 multimorbidity groups measured with Charlson Comorbidity Index (CCI), see Legend to Figure 1.

Table 2. Number of diseases from Charlson Comorbidity Index (CCI) in the study population when undergoing primary total hip arthroplasty. Values are count (%)

CCI range	0 to 10–15 [a]
CCI low	69,229
0 diseases	69,229 (100)
CCI medium	23,968
1 disease	13,999 (58)
2 diseases	9,949 (42)
CCI high	5,470
3 diseases	3,096 (57)
4 diseases	1,179 (22)
5 diseases	411 (8)
> 5 diseases	784 (14)

[a] Upper range in the study population of CCI is presented as an interval due to Danish statutory privacy restrictions. We are not allowed to publish tables or figures with numbers in single cells representing < 5 patients, or to report the values of cells if the difference between those cells can lead to the identification of patient counts < 5.

Table 3. Status on the event variable (count [%]) 0–5 years, and for 0–10 years of follow-up after undergoing primary total hip arthroplasty (THA) divided by exposure groups measured with Charlson Comorbidity Index (CCI). Values are count (%)

	CCI low	CCI medium	CCI high
0–5 years			
Censored	63,174 (91)	20,127 (84)	3,988 (73)
Aseptic loosening	548 (1)	193 (1)	43 (1)
Infection	472 (1)	246 (1)	49 (1)
Dislocation	694 (1)	325 (1)	86 (2)
Other	740 (1)	293 (1)	64 (1)
Death	3,601 (5)	2,764 (12)	1,240 (22)
Total	69,229	23,948	5,470
0–10 years			
Censored	67,328 (83)	17,226 (72)	3,249 (60)
Aseptic loosening	1,074 (2)	309 (1)	58 (1)
Infection	544 (1)	265 (1)	55 (1)
Dislocation	882 (1)	387 (2)	95 (2)
Other	1,001 (1)	345 (1)	75 (1)
Death	8,400 (12)	5,416 (23)	1,938 (35)
Total	69,229	23,948	5,470

Table 5. Estimates with 95% confidence intervals (CI) for cause-specific hazard ratios (HR), adjusted cause-specific HR (aHR), and events and risk time in person-years (p-y) for people receiving primary total hip arthroplasty (THA) due to osteoarthritis with Charlson Comorbidity Index score (CCI) medium or CCI high relative to patients receiving primary THA with CCI low

Factor	Number of events / risk time (p-y)	Crude cause-specific HR (CI)	Cause-specific aHR [a] (CI)
Any revision			
0–2 years			
CCI low	1,641/127,300	Reference	Reference
CCI medium	784/42,655	1.4 (1.3–1.5)	1.4 (1.3–1.5)
CCI high	191/9,243	1.5 (1.3–1.8)	1.5 (1.3–1.7)
0–5 years			
CCI low	2,454/282,984	Reference	Reference
CCI medium	1,057/90,949	1.3 (1.2–1.4)	1.3 (1.2–1.4)
CCI high	242/18,356	1.4 (1.2–1.6)	1.4 (1.2–1.6)
0–10 years			
CCI low	3,501/456,004	Reference	Reference
CCI medium	1,306/136,741	1.2 (1.1–1.3)	1.2 (1.2–1.3)
CCI high	283/25,032	1.3 (1.2–1.5)	1.4 (1.2–1.6)
Aseptic loosening			
0–2 years			
CCI low	252/127,300	Reference	Reference
CCI medium	100/42,656	1.2 (0.9–1.5)	1.2 (1.0–1.5)
CCI high	24/9,243	1.3 (0.9–2.0)	1.4 (0.9–2.0)
0–5 years			
CCI low	548/282,984	Reference	Reference
CCI medium	193/90,949	1.1 (0.9–1.3)	1.2 (1.0–1.4)
CCI high	43/18,356	1.2 (0.9–1.7)	1.4 (1.0–1.8)
0–10 years			
CCI low	1,074/456,004	Reference	Reference
CCI medium	309/136,741	1.0 (0.9–1.1)	1.1 (1.0–1.2)
CCI high	58/25,032	1.0 (0.8–1.4)	1.3 (1.0–1.6)
Infection			
0–2 years			
CCI low	388/127,300	Reference	Reference
CCI medium	210/42,656	1.6 (1.3–1.9)	1.5 (1.2–1.7)
CCI high	41/9,243	1.4 (1.0–1.9)	1.2 (0.9–1.6)
Dislocation			
0–2 years			
CCI low	507/127,300	Reference	Reference
CCI medium	248/42,656	1.4 (1.2–1.7)	1.4 (1.2–1.6)
CCI high	68/9,243	1.8 (1.4–2.3)	1.7 (1.3–2.2)

[a] aHR: cause-specific hazard ratio adjusted for age, sex, surgery year, and social factors such as educational level and cohabitation status.