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ORIGINAL ARTICLE

Association of influenza vaccine and risk of recurrence in patients undergoing curative surgery for colorectal cancer

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ABSTRACT

Background: There is increasing evidence that the inactivated influenza vaccine contains immunostimulatory properties that favor cytotoxicity and benefit survival in large population-based studies. This study aimed to determine whether an influenza vaccine was associated with risk of recurrence, overall mortality, and disease-free survival in patients undergoing curative surgery for colorectal cancer.

Material and methods: We performed a register-based study based in Denmark in the period 2009–2015. The primary outcome was a risk of recurrence, while the secondary outcomes were overall mortality and disease-free survival.

Results: A total of 9869 patients were included, with 5146 patients receiving an influenza vaccine between one year before and six months after surgery. In a multivariate Cox regression model, there was no association with risk of recurrence (HR 0.94, 95% CI 0.85–1.05), overall mortality (HR 0.95, 95% CI 0.87–1.03), and disease-free survival (HR 1.01, 95% CI 0.94–1.09). In patients receiving the vaccine between six and twelve months before surgery, we found an association to decreased risk of recurrence (HR 0.78, 95% CI 0.67–0.91) but no association with overall mortality (HR 1.04, 95% CI 0.93–1.17) or disease-free survival (HR 0.97, 95% CI 0.88–1.07). Subgroup analysis of patients revealed contradictory results.

Conclusion: We believe that this study's findings support the need for further clinical studies to investigate the causal effects of the influenza vaccine on oncological outcomes.

Abbreviations: CCI: Charlson comorbidity index; CRC: colorectal cancer; DCR: Danish Cancer Register; dMMR: deficient mismatch repair system; DVR: Danish Vaccination Register; ICI: immune checkpoint inhibitors; NPR: Danish National Patient Register; pMMR: proficient mismatch repair system; STROBE: the strengthening the reporting of observational studies in epidemiology; TNM: tumor (T), lymph node (N) and metastatic (M); UICC: Union for International Cancer Control

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Background

Colorectal cancer (CRC) incidence is increasing worldwide, and efforts to reduce recurrence and mortality are needed [1]. Immune checkpoint inhibitors (ICI) have recently shown promising results in the neoadjuvant setting. Patients with a deficient mismatch repair system (dMMR) experienced pathological complete response following three ICI treatments, thus underlining the potency of these treatments and the potential of including the immune system in treating cancer [2]. A new study also showed impressive results in patients with metastatic dMMR CRC treated with ICI, indicating that the treatment can also benefit patients with an increased tumor burden [3]. However, it is also evident that ICI primarily benefits the subgroup of patients with dMMR cancers, thus underlining the need to develop treatments that can benefit the majority of patients who harbor a proficient mismatch repair system (pMMR) [4].

A recent preclinical study has shown that intratumoral application of the influenza vaccine-induced changes in the tumor microenvironment concerning increased T-cell infiltration, increased local IFNγ and tumor mass reduction, and increased susceptibility of the tumors for ICI treatment [5]. Smaller clinical trials have also shown that the influenza vaccine can increase NK cell activity, a key component in eliminating cancer cells [6,7]. We have also demonstrated that in patients undergoing surgery for solid tumors receiving an influenza vaccine in the immediate post-operative period, there was an association with reduced overall- and cancer-specific mortality [8]. Thus, there is increasing evidence of a possible immunostimulatory effect of the influenza vaccine in patients with cancer. However, the influenza vaccine's possible association to recurrence, the main factor leading to death in patients with cancer [9], has not been investigated.

We hypothesized that patients undergoing curative surgery for CRC receiving an influenza vaccine before or after

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Supplemental data for this article can be accessed here.

surgery would have a reduced risk of recurrence, overall mortality, and disease-free survival. We aimed to investigate this in an observational Register-based study using a validated algorithm to determine recurrence in colorectal cancer in Danish national registers [10].

Material and methods

Study design

Patients undergoing curative surgery for colorectal cancer in Denmark in 2009–2015 were identified through the Danish National Patient Register (NPR). In NPR, all hospital contacts are registered, thus information regarding hospital admissions, such as date of entry and discharge, procedure codes, and diagnoses were obtained from NPR. All Danish residents have a unique personal identification number (CPR-number), making it possible to link data from several registers. Information regarding immigration, emigration, and mortality was obtained from the Danish Civil Registration System. This system is virtually complete with almost no loss to follow up [11]. Patients were also linked with the Danish Vaccination Register (DVR) to obtain information on any influenza vaccination date from 2009 to 2016. The level of education and income was received through Statistics Denmark. Finally, the patients were linked to the Danish Cancer Register (DCR) for information regarding tumor (T), lymph node (N), and metastatic (M) status of every patient in the cohort. Patients with metastatic disease, surgical procedures not linked to curative surgery, and incomplete pathological data were excluded. Overall mortality results of this study population were partly included in a previously published paper [8].

Variables and data sources

Cancer status was determined through the DCR, where information on the T, N, and M status of every patient was used to determine Union for International Cancer Control (UICC) status. In DCR, reporting is done automatically through linking with electronic patient journals and the nationwide pathologic database [12]. Diagnoses are based on ICD-10 codes, and pathologic data are based on SNOMED codes registered in the Danish Pathology Register (DPR). Patients with insufficient UICC data were not included in the study.

Charlson comorbidity index (CCI) was determined through NPR with an index date of ten years before surgery. We did not include any cancers in the CCI status as this was an inclusion criterion for the study, following a previously described method [13].

Education and income level were obtained through Statistics Denmark. Educational level was determined based upon the highest level of education one year before surgery. It was categorized into three standardized categories: short, defined as 7 or 9 years of mandatory primary school; medium, defined as 10–12 years of school, e.g., upper secondary school or vocational school; and long, defined as more than 12 years of education. Equivalized income level was defined as the total household income divided by household family members. It was determined considering the upper and lower quartile of income in 2010 in Denmark.

Vaccination status was determined through DVR. In Denmark, influenza vaccination is offered free of charge to all citizens belonging to risk groups, e.g., elderly of 65 or older and citizens with underlying chronic illnesses. In the study period of 2009–2015, the only trivalent inactivated influenza vaccinations were available. Information on all influenza vaccinations given as part of the national program was registered in the DVR [14]. Patients were categorized into two groups; patients who never received a vaccine and patients who received a vaccine between one year before surgery and six months after surgery. Patients in the vaccinated group were allowed to have received vaccines before one year or more than six months after surgery. The vaccinated patients were further divided according to the period of vaccination; 6–12 months before surgery, 1–6 months before surgery, 0–30 days before surgery, 0–30 days after surgery, and finally, 1–6 months after surgery.

Statistical methods

The study population was followed from 180 days postoperatively until death, loss to follow-up, or end of follow-up (31 December 2018). The study's primary outcome was the risk of recurrence, while the secondary outcomes were overall mortality and disease-free survival (time to recurrence or death). To avoid immortal time bias, we started the follow-up period 180 days after surgery for each patient.

Recurrence during follow-up was determined using a validated algorithm described in detail elsewhere [10]. One of the following criteria must be met to classify a patient as recurring:

- A specific code (DC189X and DC209X) for local colorectal cancer recurrence in the NPR any time after diagnosis. These codes have only been in use in NPR since 2012.
- SNOMED combinations indicating recurrence registered in DPR 180 or more days after the first colorectal cancer diagnosis and without a new primary cancer diagnosis.
- Metastases code registered in NPR 180 days after the first colorectal cancer surgery and without a new primary cancer diagnosis between the date of colorectal cancer surgery and the date of metastases.
- Cytostatic therapy code registered in NPR 180 or more days after first colorectal cancer surgery and 60 or more days after the last cytostatic therapy code and without a new primary tumor in the period between colorectal cancer surgery and date of cytostatic therapy.

One preplanned subgroup analysis was made. We analyzed whether stratifying for patients below or above 65 years of age affected our outcomes, as the influenza vaccine is free of charge to patients over 65 years of age.

Two preplanned sensitivity analyses were made. A tracer analysis was conducted to control for health-seeking bias, analyzing if a vaccine given outside of season did impact our

Table 1. Baseline characteristics of included patients.

Influenza vaccine	Yes (%)	No (%)
N	5146 (52.1%)	4723 (47.9%)
Sex		
Male	2730 (53.1%)	2416 (54.4%)
Age		
<60	266 (5.2%)	1610 (34.1%)
61–75	2544 (49.4%)	2276 (48.2%)
>75	2336 (45.4%)	837 (17.7%)
Timing of vaccination[a]		
6–12 m pre-op	2251 (32.6%)	
1–6 m pre-op	1848 (26.8%)	
0–30 d pre-op	261 (3.8%)	
0–30 d post-op	382 (5.5%)	
1–6 m post-op	2155 (31.2%)	
Education		
Short	2279 (44.3%)	1839 (38.9%)
Medium	1759 (34.2%)	1733 (36.7%)
Long	939 (18.3%)	1009 (21.4%)
Unknown	169 (3.3%)	142 (3.0%)
Income		
<178,800	2493 (48.6%)	1593 (34.0%)
178,800–479,000	2507 (48.9%)	2899 (61.9%)
>479,000	130 (2.5%)	190 (4.1%)
Unknown	16 (0.3%)	41 (0.9%)
CCI		
0	3160 (61.4%)	3862 (81.8%)
1–2	1648 (32.0%)	768 (16.2%)
>3	338 (6.6%)	93 (2.0%)

DKK pre-op: pre-operative; post-op: post-operative; CCI: Charlson comorbidity index.
Baseline characteristics.
[a]Calculated based upon total amounts of vaccinations (6897), as several patients received two vaccinations.

Table 2. Surgical and pathological characteristics.

Influenza vaccine	Yes (%)	No (%)
N	5146 (52.1%)	4723 (47.9%)
UICC		
1	933 (18.1%)	904 (19.1%)
2	2297 (44.6%)	1844 (39.1%)
3	1916 (37.2%)	1975 (41.8%)
Location of tumor		
Colon	3669 (71.3%)	3013 (63.8%)
Rectum	1477 (28.7%)	1710 (36.2%)
Acute or elective admission		
Elective	4488 (87.2%)	4129 (87.4%)
Acute	658 (12.8%)	594 (12.6%)
Type of surgery		
Open	3010 (58.5%)	2350 (49.8%)
Laparoscopic	2095 (40.7%)	2338 (49.5%)
Missing	39 (0.8%)	35 (0.7%)
Year of surgery		
2009	747 (14.5%)	518 (11.0%)
2010	789 (15.3%)	615 (13.0%)
2011	699 (13.6%)	620 (13.1%)
2012	708 (13.8%)	639 (13.5%)
2013	643 (12.5%)	600 (12.7%)
2014	837 (16.3%)	850 (18.0%)
2015	723 (14.1%)	881 (18.7%)

UICC: Union of International Cancer Control.
Surgical and pathological characteristics.

outcomes. The second examined whether only including patients with low comorbidities (CCI 0–2) affected outcomes.

Two *post-hoc* subgroup analyses were made. We divided patients into two groups; UICC III cancers and UICC I-II cancers to see if the cancer stage had an impact on our outcomes.

One *post-hoc* sensitivity analysis was made. As patients could receive up to two influenza vaccinations, one before and one after surgery, due to the overlapping influenza seasons, we excluded all patients receiving more than one vaccination to see if this affected our outcomes.

A Cox regression model was used in all outcome analyses. The proportional hazards assumption was evaluated by testing a time-dependent effect of vaccine status in a model that included covariates, which was significant ($p = 0.002$). Visual inspection of the proportional hazards assumption through the inverse Kaplan–Meier approach and Schoenfeld residuals (eFigure 1), however, did not indicate any major violations. Still, a visual inspection of the proportional hazards assumption did not indicate any violations. When analyzing the risk of recurrence, the competing proportional hazards model proposed by Fine and Gray was applied [15]. Results were presented as hazard ratios (HR) with 95% confidence intervals (95% CI). A *p*-value below 0.05 was considered statistically significant. Any analysis with events <5 was not reported, as this is not considered anonymized data by Statistics Denmark. Person-time was calculated until recurrence, death, or end of follow-up. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations. The study was approved by the Danish Data Protection Agency (Reg-058-2017). According to Danish Legislation, it was not a requirement to have IRB ethical approval [16]. The statistical analysis was performed using the SAS® Proprietary Software 9.4, SAS Institute Inc., Cary, NC USA.

Results

A total of 9869 patients were included in this study, with 5146 patients receiving at least one influenza vaccine (6897 vaccinations in total). To comply with the recurrence algorithm, several patients were excluded; please see eFigure 2. This excluded 531 patients from overall mortality analysis as these patients died within six months after surgery. It did not exclude any patients from the risk of recurrence analysis, as the algorithm excludes any patients with a recurrence within six months after surgery.

In Table 1, baseline characteristics are provided for the patients and surgical and pathological information in Table 2. Patients were followed for a median of 5.0 years. Please see eFigure 3 for a cumulative incidence plot stratified for influenza vaccination.

Risk of recurrence

Receiving an influenza vaccine at any time point between one year before surgery and six months after surgery did not associate with the risk of recurrence ($HR_{adjusted1}$ 0.93, 95% CI 0.83–1.03) (Table 3). When stratifying for the period of vaccine, a statistically significant association between receiving an influenza vaccine between six and twelve months before surgery and reduced risk of recurrence was found, both in unadjusted analysis and when controlling for age, sex, CCI, UICC stage, colon or rectal cancer, elective or acute surgery, year of surgery, education level and income level ($HR_{adjusted1}$ 0.78, 95% CI 0.67–0.90). This association was not found in

Table 3. Analysis of risk of recurrence in the cohort.

Influenza vaccination	Events	Person-years	IR	HR (unadjusted)	HR (adjusted1)	Competing risk model[a]
No	833	19,384	430	1 (ref)	1 (ref)	1 (ref)
Yes	856	20,349	421	0.97 (0.88–1.07)	0.94 (0.85–1.05)	0.94 (0.84–1.05)
Timing of vaccination						
6–12 m pre-op	331	8756	378	0.74 (0.64–0.86)	0.78 (0.67–0.91)	0.76 (0.65–0.89)
1–6 m pre-op	291	7203	404	0.93 (0.81–1.06)	0.93 (0.81–1.07)	0.92 (0.80–1.06)
0–30 d pre-op	40	977	409	0.93 (0.68–1.28)	0.89 (0.65–1.23)	0.89 (0.64–1.23)
0–30 d post-op	75	1574	477	1.17 (0.93–1.48)	1.06 (0.84–1.34)	1.07 (0.85–1.36)
1–6 m post-op	401	9162	438	1.21 (1.06–1.39)	1.12 (0.97–1.28)	1.13 (0.99–1.30)

IR: incidence rate per 10,000 years; HR1: adjusted for age, sex, CCI, UICC stage, colon or rectum cancer, acute or elective surgery, year of surgery, education level, and income level; pre-op: pre-operative; post-op: post-operative; CCI: Charlson Comorbidity Index; UICC: Union of International Cancer Control.
Analysis of risk of recurrence.
Patients were stratified according to the administration and period of the vaccine.
[a]Fine and gray model.

Table 4. Analysis of overall mortality in the cohort.

Influenza vaccination	Events	Person-years	IR	HR (unadjusted)	HR (adjusted1)
No	944	21,932	430	1 (ref)	1 (ref)
Yes	1597	23,154	690	1.60 (1.48–1.74)	0.94 (0.86–1.03)
Timing of vaccination					
6–12 m pre-op	737	9855	748	1.61 (1.44–1.79)	1.05 (0.94–1.17)
1–6 m pre-op	599	8117	738	1.61 (1.46–1.78)	1.00 (0.90–1.11)
0–30 d pre-op	84	1124	747	1.50 (1.21–1.87)	0.99 (0.79–1.24)
0–30 d post-op	114	1814	628	1.13 (0.93–1.36)	
1–6 m post-op	676	10,529	642	1.02 (0.92–1.14)	0.90 (0.81–1.01)

IR: incidence rate per 10,000 years; HR1: adjusted for age, sex, CCI, UICC stage, colon or rectum cancer, acute or elective surgery, year of surgery, education level, and income level; pre-op: pre-operative; post-op: post-operative; CCI: Charlson Comorbidity Index; UICC: Union of International Cancer Control.
Analysis of overall mortality.
Patients were stratified according to the administration and period of the vaccine.

other periods, but a trend in the opposite direction was noted in patients receiving the vaccine between one to six months after surgery ($HR_{adjusted1}$ 1.12 95% CI 0.97–1.28). The competing risk analysis confirmed the above results.

Overall mortality

Receiving an influenza vaccine at any time point was not associated with overall mortality ($HR_{adjusted1}$ 0.95, 95% CI 0.87–1.03) (Table 4). No association to overall mortality was evident when stratifying patients according to the period of influenza vaccination. However, a trend toward reduced overall mortality was seen in patients receiving the vaccine between one and six months after surgery ($HR_{adjusted1}$ 0.90, 95% CI 0.80–1.01).

Disease-free survival

Receiving an influenza vaccine at any time point was not associated with disease-free survival ($HR_{adjusted1}$ 1.01, 95% CI 0.94–1.09) (Table 5), nor was there any statistically significant association to disease-free survival when stratifying patients according to the period of influenza vaccination.

Subgroup and sensitivity analyses

In general, the preplanned and exploratory subgroup analyses did not differ from the main results. However, in the subgroup of patients below 65, a statistically significant association between receiving an influenza vaccine and an increased risk of recurrence, overall mortality, and worse disease-free survival was seen (eTables 1–3). The subgroup consisted of 2716 patients, of which only 19% (525 patients) received an influenza vaccine.

When excluding patients who received more than one vaccine, a decreased overall mortality was noted in patients receiving the vaccine between zero to thirty days after surgery ($HR_{adjusted1}$ 0.68 95% CI 0.49–0.95) (eTable 3) compared with unvaccinated patients.

When stratifying patients according to the UICC stage (eTables 1–3), the association to reduced risk of recurrence in patients receiving the vaccine between six to twelve months before surgery persisted in patients with UICC III cancers, while there only was a trend in patients with UICC I-II cancers. The same was evident about overall mortality, while for disease-free survival when comparing vaccine *vs*. no vaccine an association to lower disease-free survival was noted.

The remaining preplanned and exploratory sensitivity analysis did not differ from the main results (eTables 1–6).

Discussion

In this prospective register-based cohort study, we found a reduced risk of recurrence in patients receiving an influenza vaccine between six to twelve months before intended curative surgery for colorectal cancer compared to non-vaccinated patients. This was evident in both unadjusted and adjusted Cox regression models. There was no statistically significant association to overall mortality or disease-free survival in this group of patients or the whole cohort.

We have previously shown that receiving an influenza vaccine in the immediate post-operative period was associated with reduced overall- and cancer-specific mortality in patients undergoing surgery for solid tumors [8]. We cannot

Table 5. Analysis of disease-free survival in the cohort.

Influenza vaccination	Events	Person-years	IR	HR (unadjusted)	HR (adjusted1)
No	1444	19,384	745	1 (ref)	1 (ref)
Yes	2119	20,349	1041	1.39 (1.30–1.49)	1.02 (0.95–1.10)
Timing of vaccination					
6–12 m pre-op	931	8756	1063	1.24 (1.13–1.36)	0.98 (0.89–1.08)
1–6 m pre-op	767	7203	1065	1.36 (1.25–1.48)	1.03 (0.94–1.13)
0–30 d pre-op	114	977	1167	1.42 (1.17–1.71)	1.08 (0.89–1.31)
0–30 d post-op	161	1574	1023	1.18 (1.00–1.38)	1.01 (0.86–1.18)
1–6 m post-op	930	9162	1015	1.13 (1.03–1.25)	1.03 (0.93–1.13)

IR: incidence rate per 10,000 years; HR1: adjusted for age, sex, CCI, UICC stage, colon or rectum cancer, acute or elective surgery, year of surgery, education level, and income level; pre-op: pre-operative; post-op: post-operative; CCI: Charlson Comorbidity Index; UICC: Union of International Cancer Control.
Analysis of disease-free survival.
Patients were stratified according to the administration of the vaccine and the period of the vaccine.

find similar results in the primary analysis, but when excluding patients receiving more than one vaccination, we again see the statistically significant association to reduced overall mortality in patients receiving the influenza vaccine between zero to thirty days after surgery.

In recent years, the effects of unaltered influenza vaccines on the immune system have been elucidated. The early studies showed an increase in and prolonged NK cell activity after influenza vaccination that also abrogated the detrimental effects of surgery on NK cell activity [6,7]. NK cells are an essential factor in clearing cancer cells in circulation, as cancer cells lack MHC type 1 expression, the main feature that determines whether NK cells will eliminate a cell or not [17,18]. The recent preclinical studies have shown that intratumoral application of the influenza vaccine in itself can modulate the local tumor microenvironment in favor of cytotoxic immunity and its capability to 'convert' tumors to increase susceptibility to immune checkpoint inhibitors [5]. These results are encouraging and should lead to clinical studies investigating whether the influenza vaccine could be repurposed, especially when considering the safety profile of the influenza vaccine and its regular use in comorbid and immunocompromised patients [19].

Our results show that receiving an influenza vaccine well before the surgery, when cancer has not been diagnosed yet, is associated with a reduced risk of recurrence. This is, however, not accompanied by a likewise reduced overall mortality or disease-free survival. Although recurrence is a primary factor in death after colorectal cancer surgery, other events can cause death, and it would require a more extensive study population to determine this effect.

We also note with interest that the subgroup of patients with UICC III cancers seemingly is the driver of the association to a reduced risk of recurrence, as only a trend toward a reduced risk of recurrence was seen in patients with UICC I–II cancers. Stage III cancers are more susceptible to recurrence, which could be an explanation for this. Patients with stage III cancers also as a standard receive adjuvant chemotherapy, which presumably also would affect our outcomes.

This study's strengths are that we can investigate the potential effects of the influenza vaccine in a large population of patients undergoing similar procedures, which enables us to perform adjustments for potential confounders. Recurrence can be defined and diagnosed in several ways. Using the validated algorithm for determining recurrence following colorectal cancer surgery, we can provide highly reliable data on recurrences. We have also included data on education and income level, as this is known to influence survival outcomes. The registers used for this study are virtually complete as they rely on automatic registration of data from electronic patient records.

As the results are based upon an observational study, there are important limitations to consider. We show an association to increased risk of recurrence in the subgroup of patients below 65 years of age. It is evident that a number of the subgroups are with a low number of patients, which points to a power problem, but this demonstrates that the findings of this study must be investigated in clinical studies before any causal effect of the influenza vaccine on the reported outcomes can be determined. The inherent risk of residual confounding by unreported or unmeasured covariates is also present. Data on short-term complications following surgery, neoadjuvant, adjuvant treatment, and metastasis treatment and adherence to this are not present in this study. The category of the hospital has also been identified as a possible confounder even though it is not indicative of outcome [20,21]. However, in Denmark, cancer treatment is localized in specialized public hospitals, and all cancer treatments follow national guidelines, so this could be of limited effect in our analysis. However, the possible impact of these factors can be considered when considering the unadjusted and adjusted analysis of overall mortality, where the covariates included have a significant effect on the estimates. In the analysis of the risk of recurrence, however, we find that the included covariates have a negligible impact on estimates. Preliminary studies investigating the influenza vaccine in an oncological setting, also found that other vaccines had an impact on the immune system, although not as potent [6]. Information on other vaccines was not available in this study.

In conclusion, we find that receiving an influenza vaccine at any time point between one year before surgery and six months after surgery is not associated with risk of recurrence, overall mortality, or disease-free survival. In patients receiving the influenza vaccine between six to twelve months before surgery, we find an association to a reduced risk of recurrence. However, due to contradictory results in subgroup analyses, we are cautious to draw any conclusions on causality but believe that the causal effects should be investigated in clinical trials.

Disclosure statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no competing interests.

Ethical approval

Studies based solely on data from the Danish national registers do not need approval from the Danish research bioethics committees, as study participants are never contacted, and consent is not required for the use of registration information. The study's use of registered data was approved by the Danish Data Protection Agency.

Author contributions

MG and IG conceived and designed the study; defined exclusion criteria and exposure, and outcome; interpreted the study findings; and drafted the manuscript. TF and LCT assisted in data analysis, interpreted the study findings, and critically reviewed the manuscript. TGV interpreted the study findings and critically reviewed the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. MG, TF, and LCT had full access to all the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. IG is the guarantor of the study.

Transparency

The manuscript's guarantor (IG) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Data availability statement

This study is based on Danish national register data. These data do not belong to the authors but to the Danish Health Data Authority and Statistics Denmark and the authors are not permitted to share them, except in aggregate (e.g., a publication). Any research group is allowed to apply for data to the data owner which is the Danish Health Data Authority and Statistics Denmark and the data in full can then be given according to legislation after data-transfer agreements have been made.

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