Influenza Vaccination is associated with Reduced Cardiovascular Mortality in Diabetes Mellitus. A Nationwide Cohort Study.

**Authors**

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**Supplemental Material**

**EXTENDED METHODS**

**Patient characteristics**

We retrieved patient characteristics assessed at the beginning of each season (December 1) from the Danish National Patient Registry[1] using ICD-10 codes (Supplemental Table S2). All diagnoses from the Danish National Patient Register included in the Charlson comorbidity index have been validated with positive predictive values of 96% to 100%[2]. Information on medication use at the beginning of each season was retrieved from the Danish National Prescription Registry[3] and defined as at least 1 filled prescription up to 6 months prior to baseline. Household income and educational level at the beginning of each season was collected from the Danish National Population Registry[4]. To account for changes between seasons, patient age, vaccination status in previous season, comorbidities, medications and household income and were reassessed at each the beginning of each season.

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**SUPPLEMENTAL TABLES**

**Table S1.** Nationwide registries used in the present study

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **National Patient Registry** | **National Prescription Registry** | **National Population Registry** | **National Cause of Death Registry** | **National General Practitioners Reimbursement Registry** |
| **Created and established** | 1977 | 1995 | 1976 | 1970 | 1990 |
| **Examples of data in the registries** | Hospital diagnoses, hospital contacts, procedure codes | Filled prescriptions for all Danish citizens | Date of birth, sex, emigration status, household income and education level | Time and cause of death | Type and time of administration of all services in the general practice sector  |
| **Coding** | ICD-10  | ATC-codes | N/A | ICD-10  | Unique governmental reimbursement codes  |
| **Data used in the present study** | Patient comorbidities at the beginning of each season | Definition of Diabetes Mellitus and patient medication use at the beginning of each season | Age, sex, income and education level at the beginning of each season | Outcome (all-cause death, cardiovascular death, AMI and stroke death, incident cancer) and follow-up time | Vaccination exposure prior to each season  |
| **Data-linkage** | Personal identification number | Personal identification number | Personal identification number | Personal identification number | Personal identification number |

ATC; anatomical therapeutic chemical classification system. ICD-10; International Classification of Diseases 10th revision. AMI, acute myocardial infarction.

**Table S2.** Anatomical Therapeutic Chemical (ATC) Classification codes used for the definition of medication use.

|  |  |
| --- | --- |
| **Medication** | **ATC-code** |
| Statin | C10AA |
| Renin-angiotensin system inhibitor | C09 |
| Anti-thrombotic | B01 |
| Beta blocker | C07 |
| Diuretic | C03 |
| Spironolactone | C03D |
| Digoxin | C01AA05 |
| Calcium Antagonist | C08 |
| Aspirin | B01AC06 |
| Opioid | N02A |
| Antipsychotic | N05A |
| Antidepressant | N06A |
| Antiepileptic | N03A |
| Systemic glucocorticoid | H02AB |
| Proton-pump inhibitor | A02BC |
| Insulin  | A10A |
| Aspirin | B01AC06 |
| Anti-thrombotic | B01 |
| Loop diuretic  | C03CA01 |
| Metformin  | A10BA02 |
| Sulfonylurea | A10BB |
| DPP-4 inhibitor | A10BH |
| SGLT2 inhibitor | A10BK |
| GLP-1 agonist | A10BJ |
| Glitazone | A10BG |

**Table S3.** International Classification of Disease 10th revision (ICD-10) used for the definition of comorbidities.

|  |  |
| --- | --- |
| **Comorbidity** | **ICD-10 Codes** |
| Acute myocardial infarction | I21-I22 |
| Ischemic heart disease | I20-I25 |
| Valvular disease | I34-I37 |
| Cerebrovascular disease | I60-I69 |
| Systemic embolus | I26, I74 |
| Cancer | C00-C97 |
| Atrial Fibrillation or flutter | I48 |
| Heart failure | I50, I110, I130, I132 |
| Chronic renal failure | N18, I12-I13 |
| Anemia | D50, D62, D64 |
| Chronic obstructive pulmonary disease | J42, J44 |
| Peripheral vascular disease | I70, I74 |
| Liver disease | K70-K77, B150, B160, B190 |
| Rheumatic disease | M05-M06, M32-M34, M353 |
| Peptic ulcer | K25-K27, K29 |

**SUPPLEMENTAL FIGURE 1**



*Legend: Vaccination coverage, all-cause mortality rate and cardiovascular mortality rate in each season included in the study. A season denotes the period December 1 until April 1 the following year. For example, in this figure, “2007-2008” denotes the period December 1, 2007 – April 1, 2008.*

**SUPPLEMENTAL FIGURE 2**



*Legend: Landmark analyses assessing the association between influenza vaccination and outcome in each separate influenza season included in the study. In all analyses the reference is no vaccination in the given season. For each season, follow-up was counted from December 1 and ended on April 1 the next year, encompassing the period of high influenza activity in Denmark. The Cox regression models were adjusted for all variables displayed in Table 1. \*Denotes the total number of unique patients included in the study when considering all seasons*