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Higher frequency of hospitalization but lower relative mortality for pandemic influenza in people with type 2 diabetes

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Abstract. Ruiz PLD, Bakken IJ, Håberg SE, Tapia G, Hauge SH, Birkeland KI, Gulseth HL, Stene LC (Oslo University Hospital; University of Oslo; Norwegian Institute of Public Health, Oslo, Norway). Higher frequency of hospitalization but lower relative mortality for pandemic influenza in people with type 2 diabetes. *J Intern Med* 2019; https://doi.org/10.1111/joim.12984.

Background. There is limited evidence linking type 2 diabetes (T2D) to influenza-related complications.

Objectives. To test a set of research questions relating to pandemic influenza vaccination, hospitalization and mortality in people with and without T2D.

Methods. In this population-based cohort study, we linked individual-level data from several national registers for all Norwegian residents aged 30 years or more as of January 2009. People with or without T2D at baseline (n = 2 992 228) were followed until December 2013. We used Cox regression to estimate adjusted hazard ratios (aHRs).

Results. Pandemic influenza hospitalization was more common in individuals with T2D (aHR = 2.46, 95% CI 2.04–2.98). The mortality hazard ratio associated with hospitalization for pandemic influenza was lower in people with T2D (aHR = 1.82, 95% CI 1.21–2.74) than in those without T2D (aHR = 3.89, 95% CI 3.27–4.62). The same pattern was observed when restricting to 90-day mortality (aHR = 3.89, 95% CI 1.25–12.06 amongst those with T2D and aHR = 10.79, 95% CI 7.23–16.10 amongst those without T2D). The rate of hospitalization for pandemic influenza was 78% lower in those vaccinated compared to non-vaccinated amongst people with T2D (aHR = 0.22, 95% CI 0.11–0.39), whilst the corresponding estimate for those without T2D was 59% lower (aHR = 0.41, 95% CI 0.33–0.52). Mortality was 25% lower in those vaccinated compared to non-vaccinated amongst people with T2D (aHR = 0.75, 95% CI 0.73–0.77), whilst the corresponding estimate for those without T2D was 9% (aHR = 0.91, 95% CI 0.90–0.92).

Conclusions. There may have been a lower threshold for pandemic influenza hospitalization for people with T2D, rather than more severe influenza infection. Our combined results support the importance of influenza vaccination amongst people with T2D, especially during pandemics.

Keywords: diabetes mellitus, type 2, human, influenza, mortality, vaccination.

Introduction

Type 2 diabetes is a common disease [1] with an increased risk of mortality [2]. Patients with diabetes are thought to be at a higher risk of infections and postinfection complications [3–5]. Diabetes has been associated with a higher risk of influenza morbidity and mortality, but the level of evidence is low [6, 7].

In 2009–2010, the influenza A H1N1 virus infection caused a global influenza pandemic, and people with diabetes were reported to have a higher risk of hospitalization and complications after this pandemic [8]. Previous studies have assessed diabetes mainly as a risk factor for severe outcomes, such as mortality, amongst patients hospitalized with pandemic influenza [9, 10]. This interpretation is complicated by the fact that patients with diabetes

have a higher all-cause mortality compared to those without diabetes [2], even after adjustment for other prognostic factors [11]. One way to account for the higher absolute mortality in people with type 2 diabetes is to compare the mortality hazard ratio conferred by hospitalization amongst people with and without type 2 diabetes. We are not aware of previous studies using the latter approach.

In Norway, healthcare coverage is universal for all residents. The unique personal identification number allows individual-level linkage of the mandatory nationwide health registries. During the 2009–2010 pandemic, pandemic vaccination coverage was around 40% in Norway, which was higher than in most other European countries [12].

In this article, we aimed to answer the following research questions:
1 Is the risk of hospitalization with pandemic influenza higher in those with type 2 diabetes compared to those without type 2 diabetes?

2 Is the mortality hazard ratio associated with hospitalization for pandemic influenza higher amongst people with type 2 diabetes compared to the corresponding hazard ratio amongst those without type 2 diabetes?

3 What is the hospitalization hazard ratio associated with vaccination for pandemic influenza (protection from hospitalization) in people with type 2 diabetes and in those without type 2 diabetes?

4 What is the mortality hazard ratio associated with vaccination for pandemic influenza (protection from death) in people with type 2 diabetes and in those without type 2 diabetes?

The flow chart in Fig. 1 also illustrates each research question. We also estimated the pandemic influenza vaccine coverage in people with and without type 2 diabetes.

Methods

Study design and population

The study population comprised a closed cohort of all residents in Norway who were alive and 30 years or older 1 January 2009 (n = 2 992 228). Individuals were followed until death, emigration or end of study (31 December 2013). The study was approved by the Regional Ethics Committee for Medical and Health Research (REK 2010/2583).

Outcomes and exposures

The exposure and outcome for each research question are illustrated in Fig. 1. For instance, hospitalization with pandemic influenza is an exposure in research question 2 and an outcome in research question 1. The data source and definition of each of the main study variables (type 2 diabetes, pandemic influenza vaccination, hospitalization and mortality) and covariates (age, sex, education, country of birth and county of residence) are described in the following.

Data sources

Data from the National Registry were used to identify the study population. This registry contains information on vital status (date of birth, county of residence, emigration, immigration and death) from all residents in Norway. Statistics Norway provided data on country of birth and education level. The Norwegian health system is founded on the principles of universal access, and information on care is recorded in mandatory health registers. We linked individual-level data from several national health registries using the unique personal identification number. Data on diagnoses and medications were obtained from the following registers:
1 The Norwegian Patient Registry (NPR) covers all specialist health care in Norway. Reporting is mandatory, with registration as a prerequisite for reimbursement. Diagnoses are classified according to the International Classification of Diseases system (ICD-10). We obtained information on type 2 diabetes (ICD-10 code E11) and influenza (ICD-10 codes J09, J10 and J11)

2 Diagnoses from the Primary Care Database, with the International Classification of Primary Care, Second edition (ICPC-2). We obtained information on type 2 diabetes diagnoses (ICPC-2 code T90).

3 The Norwegian Prescription Database (NorPD) records date dispensed medications from pharmacies in Norway, using the Anatomical Therapeutic Chemical Classification (ATC). ATC codes A10B are used for noninsulin blood glucose-lowering drugs.

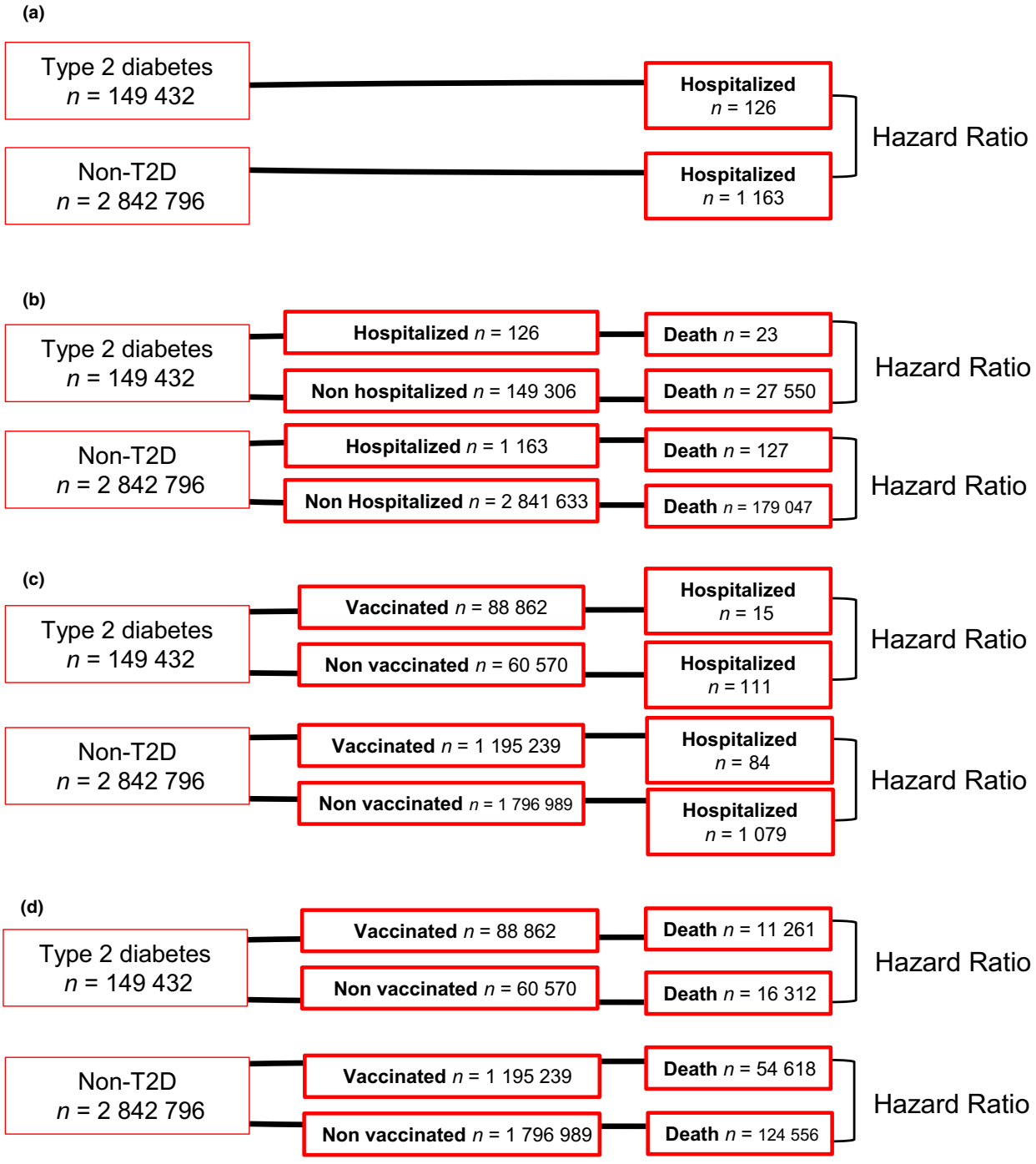

Fig. 1 *Exposures and outcomes for each research question. (a) Research question 1. Is the risk of hospitalization with pandemic influenza higher in those with type 2 diabetes compared to those without type 2 diabetes? (b) Research question 2. Is the mortality hazard ratio associated with hospitalization for pandemic influenza higher amongst people with type 2 diabetes compared to the corresponding hazard ratio amongst those without type 2 diabetes? (c) Research question 3. What is the hospitalization hazard ratio associated with vaccination for pandemic influenza (protection from hospitalization) in people with type 2 diabetes and in those without type 2 diabetes? (d) Research question 4. What is the mortality hazard ratio associated with vaccination for pandemic influenza (protection from death) in people with type 2 diabetes and in those without type 2 diabetes?*

4 SYSVAK is a national immunization registry that records individual's vaccination status. Reporting of all 2009–2010 pandemic vaccinations to the Norwegian Immunization Registry (SYSVAK) was compulsory. We obtained information on date of pandemic influenza vaccination with Pandemrix® from this registry. The pandemic influenza vaccine was available from 19 October 2009; the Norwegian Institute of Public Health recommended one single dose of vaccine to the whole population. More than 2 million vaccine doses were distributed.

Type 2 diabetes definition

Individuals were categorized as having a type 2 diabetes diagnosis on 1 January 2009 or not. Prevalent diagnosed type 2 diabetes at baseline was defined as described in detail previously [13], briefly as having either at least two registrations of a type 2 diabetes diagnosis in primary or secondary care, or at least one registration of a type 2 diabetes diagnosis (in primary or secondary care) plus registered use of noninsulin blood glucose-lowering drugs.

Pandemic influenza hospitalization and vaccination

Pandemic influenza hospitalization was defined as having a diagnosis of influenza registered in the Norwegian Patient Registry (specialist health care) during the pandemic period from May 2009 to May 2010.

The adjuvant vaccine Pandemrix® (GlaxoSmithKline) was offered to all citizens in Norway during the pandemic from 19 October 2009 through a mass vaccination campaign. The vaccine was free of charge or with a small administration fee, and risk groups were prioritized, which included people with diabetes [14]. Seasonal influenza vaccination is not mandatory to report and underreported in the immunization register, and not included in this study.

Statistical analysis

We used Cox regression analyses to estimate hazard ratios (HRs) with 95% confidence intervals (CIs), separately in people with and without T2D at baseline. Follow-up time in days from baseline (1 January 2009) was the time variable. When analysed as exposures, pandemic vaccination and hospitalization with pandemic influenza were treated as time-varying exposures. We adjusted for sex, age at baseline, education, country of birth and county of residence in the Cox regression analyses to estimate adjusted HRs (aHRs). All analyses were conducted using Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

We followed 2 992 228 individuals aged 30 years or more at baseline from 1 January 2009 to 31 December 2013. The prevalence of type 2 diabetes at baseline was 5.0% (149 432 type 2 diabetes individuals) and higher in men than in women. The prevalence strongly increased with age, ranging from 1.1% of people aged 30 to 39 years to 11.7% of people aged 80 to 89 years. We observed 206 747 deaths during 14 351 101 person-years of follow-up, 27 573 amongst those with type 2 diabetes and 179 174 amongst those without type 2 diabetes. The baseline characteristics are listed in Table 1.

Pandemic influenza vaccination coverage

Vaccination coverage was higher amongst those with type 2 diabetes (59.4%) in all age groups (Fig. 2). The coverage varied nonlinearly with age, with a similar pattern for those with and without type 2 diabetes (Fig. 2). The difference in vaccine coverage for people with and without type 2 diabetes was largest in the youngest age group. The vaccine coverage in those with type 2 diabetes ranged from 65% of people aged under 69 years to 27% of those aged over 90 years. There was an overall higher vaccine coverage in females than in males.

Hospitalization with pandemic influenza in people with and without type 2 diabetes (Research question 1)

During the pandemic period, 126 (0.08%) individuals with type 2 diabetes and 1163 (0.04%) without type 2 diabetes over 30 years were hospitalized with influenza. The largest difference was amongst the younger age group (0.18% in those with type 2 diabetes vs 0.06% in those without type 2 diabetes aged 30–39 years), and lowest difference was amongst those over 80 years (0.04% in those with type 2 diabetes vs 0.02% in those without type 2 diabetes). Hospitalization with pandemic influenza was twice as common in those with type 2 diabetes (aHR 2.46, 95% CI

Table 1. *Characteristics of the study population*

Characteristics (*n*, column percentage)	Non-type 2 diabetes over 30 years in 2009 (*n* = 2 842 796)			Type 2 diabetes over 30 years in 2009 (*n* = 149 432)		
	All	Pandemic influenza vaccination	Pandemic influenza hospitalization	All	Pandemic influenza vaccination	Pandemic influenza hospitalization
All	2 842 796	1 106 377	1163	149 432	88 862	126
Male	1 391 511 (48.9)	482 723 (43.6)	528 (45.4)	80 500 (53.9)	48 858 (55.0)	66 (52.4)
Female	1 451 285 (51.1)	623 654 (56.4)	635 (54.6)	68 932 (46.1)	40 004 (45.0)	60 (47.6)
Age, 1 January 2009						
Mean age (years)	53.2			65.2		
30–39	681 543 (24.0)	246 206 (22.3)	376 (32.3)	7204 (4.8)	4676 (5.3)	13 (10.3)
40–49	677 223 (23.8)	238 781 (21.6)	301 (25.9)	15 898 (10.6)	10 229 (11.5)	15 (11.9)
50–59	583 351 (20.5)	241 360 (21.8)	236 (20.3)	28 115 (18.8)	18 477 (20.8)	35 (27.8)
60–69	448 530 (15.8)	205 321 (18.6)	155 (13.3)	40 368 (27.0)	26 301 (29.6)	33 (26.2)
70–79	256 150 (9.0)	111 926 (10.1)	64 (5.5)	33 209 (22.2)	19 058 (21.5)	20 (15.9)
80–89	164 106 (5.8)	56 195 (5.1)	26 (2.2)	21 741 (14.6)	9 336 (10.5)	10 (7.9)
90+	31 893 (1.1)	6 588 (0.6)	5 (0.4)	2897 (1.9)	785 (0.9)	0
Education						
≤10 years	690 891 (24.3)	229 456 (20.7)	361 (31.0)	59 050 (39.5)	32 231 (36.3)	61 (48.4)
11–13 years	1 249 396 (43.9)	476 388 (43.1)	422 (36.3)	65 897 (44.1)	41 032 (46.2)	43 (34.1)
>13 years	849 227 (29.9)	392 760 (35.5)	339 (29.1)	22 564 (15.1)	14 838 (16.7)	19 (15.1)
No information	53 282 (1.9)	7 773 (0.7)	41 (3.5)	1921 (1.3)	761 (0.9)	3 (2.4)
Country of birth						
Norway	2 540 604 (89.4)	1 026 320 (92.8)	944 (81.2)	134 612 (90.1)	81 504 (91.7)	104 (82.5)
Outside Norway	302 192 (10.6)	80 057 (7.2)	219 (18.8)	14 820 (9.9)	7 358 (8.3)	22 (17.5)

2.04–2.98; unadjusted HR 2.10, 95% CI 1.75–2.52).

Hospitalization with pandemic influenza and mortality in people with and without type 2 diabetes (Research question 2)

Pandemic influenza hospitalization in people with type 2 diabetes was associated with a nearly twofold increased mortality (aHR 1.82, 95% CI 1.21–2.74), whilst the corresponding aHR in people without type 2 diabetes was 3.89 (95% CI 3.27–4.62, Table 2). The all-cause mortality within 90 days of influenza hospitalization was nearly fourfold increased in those with type 2 diabetes, whilst there was a tenfold increased mortality in those without diabetes (Table 2).

Vaccination and pandemic influenza hospitalization in people with and without type 2 diabetes (Research question 3)

Hospitalization for pandemic influenza was substantially less common amongst those vaccinated compared with those not vaccinated, both amongst those with type 2 diabetes (aHR 0.22, 95% CI 0.12–0.39) and amongst those without diabetes (aHR 0.41, 95% CI 0.33–0.52; Table 3).

Vaccination and 4-year mortality

Amongst those without type 2 diabetes, mortality during 2009–2013 was slightly lower in those who were vaccinated than in those who were not, with an aHR of 0.91, 95% CI 0.90–0.92 (Table 3). The

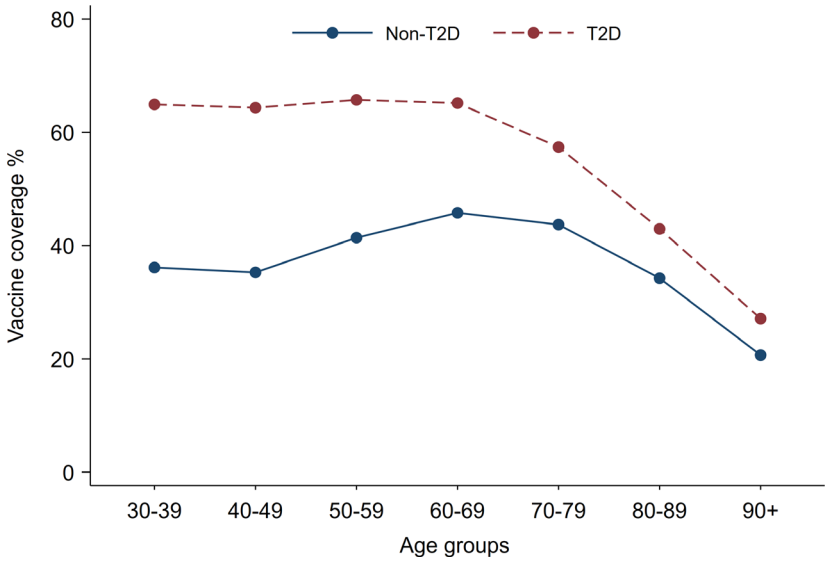

Fig. 2 *Pandemic influenza vaccination coverage in Norway by age group amongst individuals with and without prevalent type 2 diabetes during the 2009–2010 pandemic*

corresponding aHR (for vaccinated versus not) amongst people with type 2 diabetes was 0.75 (95% CI 0.73–0.77, Table 4).

Discussion

In this nationwide register-based study, we found that people with type 2 diabetes had twice the risk of hospitalization with influenza during the 2009–2010 pandemic compared to those without type 2 diabetes, but a lower relative increase in mortality associated with pandemic influenza hospitalization. Contrary to our hypothesis that those with type 2 diabetes would have more severe influenza, the latter finding suggests that there may instead have been a lower threshold for hospitalization amongst those with type 2 diabetes. Secondly, a large proportion of patients with type 2 diabetes did not comply with the recommendations to take the pandemic vaccine during the mass vaccination campaign. Thirdly, pandemic vaccination was associated with a stronger relative decrease in the risk of both hospitalization with pandemic influenza and mortality in people with type 2 diabetes compared to people without type 2 diabetes.

Strengths and limitations

This was a study with nearly complete nationwide coverage of registered individuals with type 2 diabetes over 30 years of age and a large number of deaths over a 5-year period. The strength of our study is that we obtained information about prevalent type 2 diabetes from independent registers, whereas cause of death registry data is insufficient because diabetes is frequently not mentioned in the death certificates [15]. We focused on all-cause mortality as our primary outcome, because influenza is rarely coded as an underlying cause of death, likely because of different clinical symptoms and lack of laboratory confirmation before death [16]. We focused on hospitalization with pandemic influenza, rather than any influenza illness, because the large majority of illnesses were mild and self-limiting and required no contact with the healthcare system [17]. The Norwegian Patient Registry covers nearly all hospital care in Norway, and there was a massive focus on influenza during the pandemic. We therefore believe that the validity was reasonable. However, no formal validation has been performed, and we cannot exclude the possibility that some cases were misclassified. Pandemic vaccination registration was mandatory and nearly complete. The algorithm for type 2 diabetes is based on combining three independent registers [13] and is likely to ensure the majority of type 2 diabetes cases. Still, we cannot rule out a small risk of misclassification. On the other hand, we lacked clinical data, disease duration, diabetes-related complications or information on glycaemic

Table 2. *Association of hospitalization for the 2009–2010 pandemic influenza, with mortality during 2009–2013, in people with and without type 2 diabetes*

	No. of deaths	Mortality rate (95% CI)[a]	Unadjusted hazard ratios (95% CI)	Adjusted hazard ratios (95% CI)[b]
People with type 2 diabetes				
Hospitalization with pandemic influenza				
Yes	23	47.4 (31.5–71.4)	1.14 (0.76–1.72)	1.82 (1.21–2.74)
90-day mortality after hospitalization[c]	3	96.7 (31.2–299.9)	2.41 (0.78–7.46)	3.89 (1.25–12.06)
No	27 550	40.8 (40.3–41.3)	1 (reference)	1 (reference)
People without type 2 diabetes				
Hospitalization with pandemic influenza				
Yes	127	27.8 (23.4–33.1)	2.11 (1.78–2.51)	3.89 (3.27–4.62)
90-day mortality after hospitalization[c]	24	83.5 (55.9–124.5)	6.48 (4.34–9.67)	10.79 (7.23–16.10)
No	179 047	13.1 (13.0–13.2)	1 (reference)	1 (reference)

[a]Deaths per 1000 person-years
[b]Adjusted for age at baseline in 10-year categories, sex, county of residence and country of birth (Norway or not).
[c]Subgroup analysis.

Table 3. *Pandemic influenza vaccination and risk of hospitalization with pandemic influenza, in people with and without type 2 diabetes*

	No. of hospitalized patients	Unadjusted hazard ratios	Adj. hazard ratios (95% CI)[a]
People with type 2 diabetes			
Pandemic influenza vaccination			
Yes	15	0.23 (0.13–0.40)	0.22 (0.12–0.39)
No	111	1 (reference)	1 (reference)
People without type 2 diabetes			
Pandemic influenza vaccination			
Yes	84	0.40 (0.32–0.50)	0.41 (0.33–0.52)
No	1079	1 (reference)	1 (reference)

[a]Adjusted for age at baseline in 10-year categories, sex, county of residence and country of birth (Norway or not).

control, as well as a data on risk factors affecting both mortality and diabetes (or influenza) such as obesity and smoking habits, and were thus unable to adjust for these as potential confounding factors. However, patients with diabetes in the current study are likely to represent the full spectrum of variation in the population.

Vaccination

Although individuals with type 2 diabetes in our study had higher vaccination coverage than the general population, more than 40% were not vaccinated. Vaccination coverage decreased with age, and as a large proportion of the unvaccinated individuals were elderly, more frail individuals could partially explain the association of vaccination with reduced mortality [18]; however, our results are adjusted for age. Unvaccinated individuals were not more frail than vaccinated individuals in a Danish study [19]. In Norway, with a similar health system as Denmark, the vaccination was broadly available and recommended to all age groups. We did not have adequate data on seasonal influenza vaccination, but we have assumed that earlier seasonal influenza vaccination would not confer immunity to the pandemic influenza. Use of antiviral medications is lacking as these drugs were available over the counter during the pandemic and not registered in the prescription database, but we do not expect the use of these to differ between individuals with and without diabetes.

Table 4. *Association of vaccination for the 2009–2010 pandemic influenza, with mortality during 2009–2013, in people with and without type 2 diabetes*

	No. of deaths	Mortality rate (95% CI)[a]	Unadjusted hazard ratios (95% CI)	Adjusted hazard ratios (95% CI)[b]
People with type 2 diabetes				
Pandemic influenza vaccination				
Yes	11 261	32.3 (31.7–32.9)	0.57 (0.55–0.58)	0.75 (0.73–0.77)
No	16 312	49.8 (49.1–50.6)	1 (reference)	1 (reference)
People without type 2 diabetes				
Pandemic influenza vaccination				
Yes	54 618	12.2 (12.1–12.3)	0.89 (0.88–0.90)	0.91 (0.90–0.92)
No	124 556	13.5 (13.4–13.6)	1 (reference)	1 (reference)

[a]Deaths per 1000 person-years.
[b]Adjusted for age at baseline in 10-year categories, sex, county of residence and country of birth (Norway or not).

The Nordic countries had the highest pandemic vaccination coverage in Europe [12]. Pandemic influenza vaccine coverage amongst individuals with diabetes was reported in few studies [18, 20], studies on seasonal influenza coverage amongst individuals with diabetes showed coverage rates around 50–60% [21, 22]. Vaccination and influenza diagnosis may reflect healthcare use habits [23]. Influenza vaccination in people with diabetes has been found to significantly reduce influenza- and diabetes-related hospital admissions [6], in accordance with our results. Based on observational studies, the estimated protective effects of vaccination seem to be similar in individuals with diabetes compared to individuals without diabetes [24–27].

Mortality after hospitalization for pandemic influenza

Type 2 diabetes was associated with an increased risk of hospitalization, consistent with other studies [10, 28]. The relative increase in mortality after hospitalization with pandemic was lower in people with type 2 diabetes compared with individuals with type 2 diabetes. Our a priori hypothesis was that people with type 2 diabetes had a higher risk of hospitalization and mortality with pandemic influenza, because of more severe infections in this group. The lower mortality suggests that the increased risk may instead have been due to a different policy or lower threshold of disease severity for hospitalization of people with diabetes.

Conclusion

Individuals with type 2 diabetes were more likely to be hospitalized with pandemic influenza, whilst the relative mortality after hospitalization was lower in this group. This suggests that there may have been a lower threshold for hospitalization for pandemic influenza of people with type 2 diabetes, rather than more severe influenza infection. The results highlight the importance of influenza vaccination of people with type 2 diabetes, particularly during influenza pandemics.

Acknowledgement

Data from the Norwegian Patient Register have been used in this study. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian patient register is intended nor should be inferred.

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Conflict of interest statement

HLG reports personal fees and other fees from Novo Nordisk, personal fees from Sanofi-Aventis, personal fees from MSD, outside the submitted work.

None of the other authors has any conflict of interests to declare.

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