Vaccine: X 14 (2023) 100336

Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

Diabetes incidence before and after COVID-19 vaccination – Results from the German Disease Analyzer database

Bernd Kowall [a,*], Karel Kostev [b], Rüdiger Landgraf [c], Hans Hauner [d], Ralf Bierwirth [e], Oliver Kuss [f,g], Wolfgang Rathmann [f]

[a] Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, Germany
[b] Epidemiology, IQVIA, Frankfurt/Main, Germany
[c] German Diabetes Foundation, Munich, Germany
[d] Institute of Nutritional Medicine, School of Medicine, Technical University of Munich, Munich, Germany
[e] MVZ Praxis für Diabetologie, Essen, Germany
[f] Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Germany
[g] Centre for Health and Society, Faculty of Medicine, Heinrich Heine University Düsseldorf, Germany

ARTICLE INFO

Keywords:
Diabetes mellitus
COVID-19
SARS-CoV-2
Vaccination

ABSTRACT

Objective: We investigated whether COVID-19 vaccination had an impact on diabetes risk.
Methods: We used data of 6,198 patients (mean age 64.3 years) from the nationwide Disease Analyzer database, a representative panel of physicians' practices in Germany. Patients received their first COVID-19 vaccination between 1 April 2021 and 31 March 2022, and all were newly diagnosed with diabetes within 183 days before or after this vaccination. Incident rates of diabetes after vaccination were compared to incident rates before vaccination.
Results: The incidence rate of diabetes was lower after vaccination than before vaccination (incidence rate ratio = 0.79, 95% confidence interval: 0.75–0.83). The number of incident cases of diabetes was not greater in 2021 than in 2019.
Conclusion: Our study did not confirm an increased risk of diabetes after COVID-19 vaccination. Further studies are needed to show whether the vaccination may be associated with a reduced diabetes risk.

Introduction

It is well established that the risk of diabetes increases after SARS-CoV-2 infection [1–3]. This is in marked contrast to the conflicting evidence on the risk of diabetes after COVID-19 vaccination. There have been several case reports of acute onset of type 1 diabetes following COVID-19 vaccination [4]. Apart from case reports, there are few studies on the short-term effects of the COVID-19 vaccination on glycaemia [5–7]. Two studies –one in people with either type 1 or type 2 diabetes, one in children and adolescents with type 1 diabetes – reported no short-term change in glycaemic control after COVID-19-vaccination [5,6]. Another study suggested that COVID-19 vaccination can cause temporary instability of glycaemic control in type 1 diabetes [7]. Analysis of population-based registry data in China suggested that COVID-19 vaccination had no effect on the incidence of type 1 diabetes in 2021 [8]. Finally, a recent retrospective study found that the risk of diabetes after COVID-19 infection was lower in vaccinated than in unvaccinated persons [9].

A randomised controlled trial, which would be the best design to investigate the causal effects of COVID-19 vaccination on glucose metabolism, would not be ethically justifiable. The problem with using retrospective data to compare vaccinated and unvaccinated people is that these two groups differ substantially in characteristics that are rarely assessed. Unvaccinated people have been shown to have less trust in medical experts, less external locus of control, and less fear of COVID-19 than vaccinated people [10]. In this study, we used only incident diabetes cases and compared periods after vaccination to periods before vaccination in the same person.

* Corresponding author at: Institute of Medical Informatics, Biometry and Epidemiology (IMIBE), University Hospital Essen, Hufelandstraße 55, 45147 Essen, Germany.
E-mail address: bernd.kowall@uk-essen.de (B. Kowall).

https://doi.org/10.1016/j.jvacx.2023.100336
Received 13 April 2023; Received in revised form 7 June 2023; Accepted 19 June 2023
Available online 24 June 2023

Methods

We used data from the Disease Analyzer database, which comprises a representative panel of physicians' practices in Germany [11]. The database is representative of general and specialist practices in Germany, and prevalence and incidence of chronic diseases are largely consistent with national data [12]. Data on diseases (ICD-10) and treatments (ATC codes) are transmitted directly from the practice computers.

This study included 6,198 patients (52.6% men, mean age 64.3 years (standard deviation 13.2), age range 7–98 years) from 970 practices, who received a first dose of a COVID-19 vaccine between April 1st 2021 and March 31st 2022, and who were all newly diagnosed with diabetes no more than 183 days before or after this vaccination. Further inclusion criteria were entries into the database in the time range of 730 days before to 183 days after vaccination, and no diagnosis of COVID-19 during this time period.

Characteristics of patients with newly diagnosed diabetes were reported separately by time of diagnosis. Values refer to the six months before (after) first vaccination depending on whether diabetes was diagnosed before or after first vaccination. We estimated incidence rate ratios (IRRs) with 95% confidence intervals to compare the incidence rates of diabetes after and before the first vaccination. The day of vaccination was excluded from the analyses. In an additional analysis, we compared the overall monthly numbers of incident cases of diabetes in the 970 practices (irrespective of the vaccination) in 2021 with the corresponding numbers in 2019. We have not used 2020 for comparison because routine health care may have been disrupted in that year [13,14]. Analyses were carried out using SAS 9.4 (SAS Institute, Cary, USA).

Results

Patients with a new diagnosis of diabetes during the six months before first COVID-19 vaccination and patients with a new diagnosis of diabetes during the six months after first COVID-19 vaccination were similar in age, sex, BMI, HbA1c, and prescription of glucose-lowering drugs (Table 1). Patients with a new diagnosis of diabetes before vaccination had an average number of 4.6 primary care visits during the six months before vaccination, as compared to 3.3 visits during the six months after vaccination in those with a new diagnosis of diabetes after vaccination.

Most people were included in April and May 2021, afterwards the number of people with a first vaccination decreased strongly. The incidence rate of diabetes was lower after than before vaccination (IRR = 0.79, 95% CI: 0.75–0.83). This difference was observed for all months except October and December 2021 (Table 2). On the day of the vaccination, the number of incident diabetes cases was increased compared to previous and following time periods (n = 246). There were consistently higher numbers of incident cases of diabetes before vaccination over the whole study period: 640 vs 496 incident cases in the 1–30 days before and after vaccination; 508 vs 455 (31–60 days); 536 vs 440 (61–90 days); 549 vs 368 (91–120 days); 493 vs 388 (121–150 days); 535 vs 419 days (151–180 days), respectively. IRR for type 1 diabetes was 0.93, 95%CI: 0.69–1.24) (n = 193). For type 2 diabetes (n = 4,417: 0.78, 0.73–0.82) and unspecified diabetes (n = 1556: 0.79, 0.71–0.87) IRR were both decreased.

In the 970 practices, there were only few and small differences in the monthly numbers of incident cases of diabetes in 2021 compared to 2019 (Fig. 1).

Discussion

The present study showed that the risk of incident diabetes was not increased following COVID-19 vaccination. The rate of incident diabetes in the six months after the first vaccination was 20% lower compared to the six months before vaccination. In the 970 practices which regularly transferred data to the Disease Analyzer, the number of incident cases of diabetes was not larger in 2021 than in 2019. The effect of the vaccination on the risk of diabetes was stronger in type 2 than in type 1 diabetes. However, the number of patients with type 1 diabetes was small (n = 193), and, thus, the estimate of the incidence rate of diabetes in type 1 diabetes was rather imprecise.

Our data suggest that Covid-19 immunization may reduce diabetes risk. But in the view of lacking data on effects of vaccination on insulin secretion, insulin sensitivity or immune system modulation further studies are necessary to investigate this association. Moreover, the following two reasons may partly explain why the incidence of diabetes was lower after the first vaccination:

First, people with newly diagnosed diabetes were more likely to get early vaccination. Shortly after onset of the pandemic, it was reported that patients with diabetes had a higher risk of severe outcomes and excess mortality related to COVID-19 [15]. Early vaccination was

Table 1
Characteristics of people with newly diagnosed diabetes six months before or after receiving the first dose of Covid-19 vaccine: Disease Analyzer database (2019–2021).

		Total	Diagnosis of diabetes during	
			6 months before first vaccination [a]	6 months after first vaccination [b]
N		6,198	3,579	2,619
Age (years) (mean, SD)		64.3 (13.2)	64.3 (13.1)	64.2 (13.4)
Sex (male (N, %))		3260 (52.6)	1896 (53.0)	1364 (52.1)
BMI (kg/m^2) (mean, SD)		31.4 (5.9) N = 700	31.4 (5.7) N = 410	31.5 (6.3) N = 290
HbA1c [%] (mean, SD)		7.0 (1.5) N = 3360	7.1 (1.6) N = 1970	7.0 (1.4) N = 1390
Fasting blood glucose (mg/dl) (mean, SD)		145.0 (62.4) N = 3159	148.7 (64.6) N = 1817	139.8 (58.7) N = 1342
Visits to the doctor (mean, SD)		7.9 (4.9)	4.6 (5.5)	3.3 (4.9)
Treatment prevalence (N, %)	Hypertension	2756 (44.5)	1621 (45.3)	1135 (43.3)
	Obesity	571 (9.2)	327 (9.1)	244 (9.3)
	Lipid disorders	1494 (24.1)	880 (24.6)	614 (23.4)
	Myocardial infarction	159 (2.6)	83 (2.3)	76 (2.9)
	Stroke	119 (1.9)	72 (2.0)	47 (1.8)
	Venous thromboembolism	42 (0.7)	27 (0.8)	15 (0.6)
Prescription of glucose-lowering drugs (N, %)	Insulin	710 (11.5)	426 (11.9)	284 (10.8)
	Sulphonylureas	99 (1.6)	67 (1.9)	32 (1.2)
	Biguanides	2304 (37.2)	1359 (38.0)	945 (36.1)
	DDP-4 inhibitors	639 (10.3)	397 (11.1)	242 (9.2)
	SGLT2 inhibitors	603 (9.7)	330 (9.2)	273 (10.4)
	GLP-1 receptor agonists	217 (3.5)	114 (3.2)	103 (3.9)
	Corticosteroids	308 (5.0)	156 (4.4)	152 (5.8)

[a] −183 to 0 days relative to day of first Covid-19 vaccination.
[b] 1 to 183 days relative to day of first Covid-19 vaccination.

Table 2
Numbers of newly diagnosed diabetes cases, and incidence rate ratios (with 95% confidence intervals) for newly diagnosed diabetes six months before and after COVID-19 vaccination: Disease Analyzer database (Germany).

Period of vaccination	Newly diagnosed cases of diabetes (stratified by the date of diagnosis relative to the date of vaccination)			IRR (95% CI) [a, b]
	Days −183 to −1 (Diagnosis before vaccination)	0 (Diagnosis on the day of vaccination)	Days 1 to 183 (Diagnosis after vaccination)	
April 2021 to March 2022	**3333**	**246**	**2619**	**0.786 (0.747–0.827)**
April 2021[c]	1316	101	978	0.743 (0.684–0.807)
May 2021	847	57	611	0.721 (0.650–0.800)
June 2021	477	38	398	0.834 (0.730–0.953)
July 2021	254	17	205	0.807 (0.671–0.970)
August 2021	112	9	92	0.821 (0.623–1.082)
September 2021	83	4	85	1.024 (0.757–1.386)
October 2021	51	8	61	1.196 (0.825–1.735)
November 2021	76	2	72	0.947 (0.686–1.308)
December 2021	66	3	73	1.106 (0.793–1.543)
January to March 2022	51	7	44	0.863 (0.576–1.291)

IRR: incidence rate ratio; CI: confidence interval.
[a] without day of vaccination.
[b] reference: time period before vaccination.
[c] How to read: From all patients with a first COVID-19 vaccination in April 2021 with a diagnosis of diabetes 6 months before or after the vaccination, 1316 had the diagnoses of diabetes before the vaccination, and 978 had it after the vaccination.

therefore recommended for people with diabetes, who should be given priority at the start of the vaccination campaign [16]. In line with this recommendation, more people were vaccinated exactly on the day of the diagnosis of diabetes, most likely as a consequence of diagnosis. However, the excess of new diagnoses of diabetes on days of vaccination was limited. For example, in April 2021, there were 2,395 new diagnoses of diabetes, 101 of which took place on the days of vaccination. Without association with the vaccination, about 80 diagnoses per day (2,395 / 30) would be expected. Second, the lower rate of diabetes incidence after the first COVID-19 vaccination may partly be explained by the slightly lower numbers of in-person visits to the doctor in those with a diagnosis after vaccination.

Because the diagnosis of diabetes had an impact on the exposure to COVID-19 vaccine, conclusions about the effect of vaccination on diabetes incidence can only be drawn with caution. Nevertheless, the large reduction in diabetes incidence after vaccination makes a strong positive causal effect of the COVID-19 vaccination on the diabetes risk rather unlikely. This is consistent with our observation that the monthly numbers of incident diabetes cases in 2021 were little different from the numbers in 2019.

In a recent retrospective cohort study with a self-controlled exposure-crossover design, the risk of incident diabetes was considerably larger in unvaccinated than in vaccinated persons [8]. However, the authors did not discuss whether they considered this reduction as a causal effect of the vaccination.

A strength of our study is the large study sample based on a representative practice panel with real world data. Moreover, we used a case-only design so that confounders not changing over time have no influence on the results. As the vaccination campaign in medical practices in Germany did not start until April 2021, we included almost all persons with a first vaccination and incident diabetes in the six months before or after the vaccination in our practice sample. Some limitations have to be mentioned. Aging during the observation period was not taken into account. However, the small age difference of six months between observation after and before the vaccination can be assumed to have a negligible influence on the results. Furthermore, BMI, HbA1c and fasting glucose were not available for all patients: GPs documented BMI only for few patients, and not all practices transmitted laboratory values to the

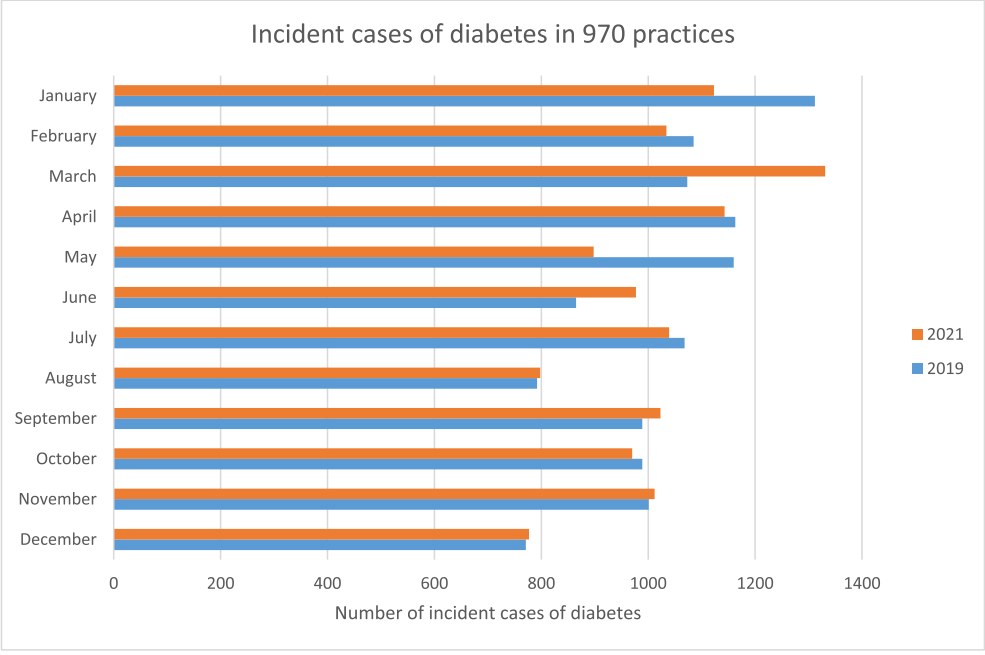

Fig. 1. Overall monthly numbers of incident cases of diabetes in 970 practices (2021 vs 2019): the German Disease Analyzer database. The numbers refer to all patients with newly diagnosed diabetes in the 970 practices irrespective of vaccination.

German Disease Analyzer. Finally, we had no information on the type of COVID-19 vaccines used.

In conclusion, our study suggests that the COVID-19 vaccine does not increase the risk of diabetes. Further studies are needed to show whether the vaccination is even associated with reduced diabetes risk.

Funding

This study was funded by the German Diabetes Foundation (Deutsche Diabetes Stiftung).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

References

[1] Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after Covid-19. Diabetologia 2022;65(6):949–54.
[2] Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. Lancet Diabetes Endocrinol. 2022;10(5):311-21.
[3] Rezel-Potts E, Douiri A, Sun X, Chowienczyk PJ, Shah AM, Gulliford MC, et al. Cardiometabolic outcomes up to 12 months after COVID-19 infection. A matched cohort study in the UK. PLoS Med 2022;19(7).
[4] Pezzaioli LC, Gatta E, Bambini F, Facondo P, Gava M, Cavadini M, et al. Endocrine system after 2 years of COVID-19 vaccines: A narrative review of the literature. Front Endocrinol (Lausanne) 2022;13.
[5] Aberer F, Moser O, Aziz F, Sourij C, Ziko H, Lenz J, et al. Impact of COVID-19 vaccination on glycemia in individuals with type 1 and type 2 diabetes: substudy of the COVAC-DM Study. Diabetes Care 2022;45(2):e24–6.
[6] Gouda N, Dimitriadou M, Sotiriou G, Christoforidis A. The impact of COVID-19 vaccination on glycaemic control in children and adolescents with type 1 diabetes mellitus on continuous glucose monitoring. Acta Diabetol 2022;59:1609–14.
[7] Heald AH, Stedman M, Horne L, Rea R, Whyte M, Gibson JM, et al. The change in glycaemic control immediately after COVID-19 vaccination in people with type 1 diabetes. Diabet Med 2022;39:e14774.
[8] Liu C, Guo MN, Chai Z et al. Association between Covid-19 vaccination and incidence of type 1 diabetes in China: evidence from 14.14 million registered residence between 2007 and 2021. Diabetes Res Clin Pract 2023; doi: 10.1016/j.diabres.2023.110723.
[9] Kwan AC, Ebinger JE, Botting P, Navarrette J, Claggett B, Cheng S. Association of COVID-19 vaccination with risk for incident diabetes after COVID-19 infection. JAMA Netw Open 2023;6(2):e2255965.
[10] Kaliterna Lipovčan L, Prizmić-Larsen Z, Franc R. Differences between COVID-19-vaccinated and unvaccinated participants from Croatia. Croat Med J 2022;63(6):508–14.
[11] Rathmann W, Bongaerts B, Carius H-J, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer Database. Int J Clin Pharmacol Ther 2018;56(10):459–66.
[12] Becher H, Kostev K, Schröder-Bernhardi D. Validity and representativeness of the "Disease Analyzer" Patient Database for use in pharmacoepidemiological and pharmacoeconomic studies. Int J Clin Pharmacol Ther 2009;47(10):617–26.
[13] Valabhji J, Barron E, Gorton T, Bakhai C, Kar P, Young B, et al. Associations between reductions in routine care delivery and non-COVID-19-related mortality in people with diabetes in England during the COVID-19 pandemic: a population-based parallel cohort study. Lancet Diabetes Endocrinol 2022;10(8):561–70.
[14] Carr MJ, Wright AK, Leelarathna L, Thabit H, Milne N, Kanumilli N, et al. Impact of COVID-19 restrictions on diabetes health checks and prescribing for people with type 2 diabetes: a UK-wide cohort study involving 618161 people in primary care. BMJ Qual Saf 2022;31(7):503–14.
[15] Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19 related mortality in England: a whole population study. Lancet Diabetes Endocrinol 2020;8(10):813–22.
[16] Pal R, Bhadada SK, Misra A. COVID-19 vaccination in patients with diabetes mellitus: Current concepts, uncertainties and challenges. Diabetes Metab Syndr 2021;15(2):505–8.

DOI: 10.1016/j.jvacx.2023.100336
URN: urn:nbn:de:hbz:465-20230911-154012-6