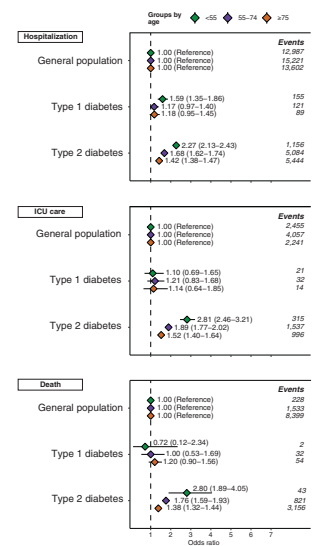
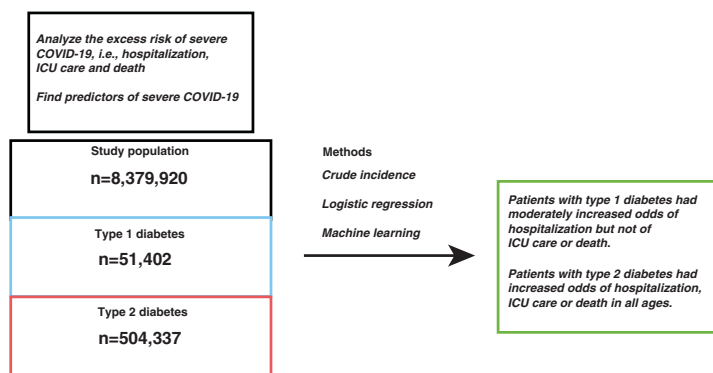


## Severe COVID-19 Infection in Type 1 and Type 2 Diabetes During the First Three Waves in Sweden

Jon Edqvist, Christina Lundberg, Karin Andreasson, Lena Björck, Pigi Dikaiou, Johnny Ludvigsson, Marcus Lind, Martin Adiels, and Annika Rosengren

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Severe coronavirus disease 2019 (COVID-19) infection in type 1 and type 2 diabetes during the first three waves of the pandemic in Sweden. ICU, intensive care unit.



### ARTICLE HIGHLIGHTS

- While type 2 diabetes is an established risk factor for severe coronavirus disease 2019 (COVID-19), findings with respect to type 1 diabetes have been conflicting.
- We aimed to study the excess risk of severe COVID-19 among patients with type 1 and type 2 diabetes compared with a control population without diabetes.
- Patients with type 2 diabetes had an increased risk for all severe COVID-19 outcomes, while patients with type 1 diabetes had no excess risk of need of intensive care or death.
- Type 1 diabetes in Sweden was not associated with excess risk of need of intensive care for COVID-19 or death.



# Severe COVID-19 Infection in Type 1 and Type 2 Diabetes During the First Three Waves in Sweden

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## OBJECTIVE

Type 2 diabetes is an established risk factor for hospitalization and death in COVID-19 infection, while findings with respect to type 1 diabetes have been diverging.

## RESEARCH DESIGN AND METHODS

Using nationwide health registries, we identified all patients aged  $\geq 18$  years with type 1 and type 2 diabetes in Sweden. Odds ratios (ORs) describe the general and age-specific risk of being hospitalized, need for intensive care, or dying, adjusted for age, socioeconomic factors, and coexisting conditions, compared with individuals without diabetes. Machine learning models were used to find predictors of outcomes among individuals with diabetes positive for COVID-19.

## RESULTS

Until 30 June 2021, we identified 365 (0.71%) and 11,684 (2.31%) hospitalizations in 51,402 and 504,337 patients with type 1 and 2 diabetes, respectively, with 67 (0.13%) and 2,848 (0.56%) requiring intensive care unit (ICU) care and 68 (0.13%) and 4,020 (0.80%) dying (vs 7,824,181 individuals without diabetes [41,810 hospitalizations (0.53%), 8,753 (0.11%) needing ICU care, and 10,160 (0.13%) deaths]). Although those with type 1 diabetes had moderately raised odds of being hospitalized (multiple-adjusted OR 1.38 [95% CI 1.24–1.53]), there was no independent effect on ICU care or death (OR of 1.21 [95% CI 0.94–1.52] and 1.13 [95% CI 0.88–1.48], respectively). Age and socioeconomic factors were the dominating features for predicting hospitalization and death in both types of diabetes.

## CONCLUSIONS

Type 2 diabetes was associated with increased odds for all outcomes, whereas patients with type 1 diabetes had moderately increased odds of hospitalization but not ICU care and death.

Since the severe acute respiratory syndrome coronavirus 2 (the virus that causes coronavirus disease 2019 [COVID-19]) infection began spreading worldwide, virtually all nations have experienced strained health care systems and many deaths, although Sweden experienced comparatively low excess mortality during the COVID-19 pandemic (1). From the outset, type 2 diabetes has been recognized as a strong risk factor for severe outcomes in COVID-19, along with coexisting conditions, obesity, and

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inflammatory responses (2). Although patients with type 1 diabetes have been found to have increased in-hospital mortality (3), findings regarding fatal cases among patients with type 1 diabetes have been heterogeneous, ranging from no statistically increased risk of death with COVID-19 (4) to a worse prognosis among patients with confirmed COVID-19 infection and type 1 diabetes compared with those with type 2 or no diabetes (5). In a report from the first few months of the pandemic through 17 August 2020, only 21 deaths were identified among 44,639 people with type 1 diabetes registered in the Swedish National Diabetes Register. Although their odds of dying were approximately threefold after adjustment for age and sex, no independently raised odds of death persisted after multivariable adjustment, and there was no death in patients with type 1 diabetes aged <45 years. In the current study, using data from administrative registries for the entire adult Swedish population alive on 1 January 2020 with follow-up until June 2021, we aimed to evaluate the risk of COVID-19–related hospitalization, intensive care unit (ICU) care, and death among individuals with type 1 diabetes and type 2 diabetes compared with the population without diabetes. A secondary aim was to find predictors of severe COVID-19 among patients with type 1 diabetes and type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Data Sources and Study Population

The Population Register, held by Statistics Sweden, registers all Swedish citizens. Data from the Swedish Patient Register and the Swedish Prescribed Drug Register were linked to The Population Register through the unique Swedish personal identity number for all individuals aged  $\geq 18$  years in order to classify them as with and without diabetes. Diabetes, comorbidities, and deaths were defined according to the ICD-8, ICD-9, and ICD-10 (Supplementary Table 1 lists the codes used). We identified 8,390,008 individuals alive and living in Sweden as of 1 January 2020. Individuals with a registered diabetes diagnosis not classified as type 1 or type 2 were excluded ( $n = 10,086$ ), as were individuals with inconsistent COVID-19 registration ( $n = 2$ ). Data on country of birth (defined as Nordic [Sweden, Denmark, Finland, Norway, and Iceland] and all other countries) and education

(defined as  $\leq 9$ , 10–12 years, and university) were collected from Statistics Sweden (Supplementary Fig. 1).

Data on need of care were retrieved from the registry of municipal care kept by the National Board of Health and Welfare. Need of care was defined in the following order: long-term-care facility if the type of living was defined as special housing; home care if an individual had home care; and independent living if no registration for long-term-care facility or home care. Personal identifiers were removed after linkage of the registries and replaced by a code. Because pseudonymized data were used, written informed consent was not applicable. The project was approved by the Swedish Ethical Review Authority (2020–02019).

### Diabetes Classification

The Swedish Patient Register was used to obtain diagnoses for patients with a registered diabetes code in either in-hospital or hospital outpatient care using ICD-10 codes E10 (type 1 diabetes) and E11 (type 2 diabetes). Patients with type 1 diabetes are routinely managed in hospital-based care at onset and at regular intervals after onset. To identify patients treated in primary care or with conflicting information with respect to ICD-10 codes E10 and E11, we used data from the Swedish Prescribed Drug Register, which provided information on filled prescriptions for medications defined as oral glucose-lowering agents or exogenous insulin in 2019. For detailed diabetes classification, see Supplementary Fig. 2. Age at onset was calculated by using the individual's earliest registered diabetes diagnosis in the Swedish Patient Register, including ICD-8, ICD-9 (250), and ICD-10 codes.

### Outcomes

COVID-19 infection was defined as a positive PCR test. Three outcomes related to severe COVID-19 were defined: 1) Hospitalization was defined as a hospital discharge diagnosis of U07.1 or U07.2; 2) ICU care was defined as a hospital-registered administration code of high-flow oxygen or ventilator use in the Swedish Patient Register (Supplementary Table 2) or the Swedish Intensive Care Register (contains complete coverage of patients admitted to the ICU); and 3) death was defined as COVID-19 being the underlying or contributory cause of death (the latter only

in patients with predefined COVID-19–related underlying cause of death [see Supplementary Table 2 for acceptable diagnoses]). Both in-hospital and out-of-hospital deaths were identified.

### Statistical Analyses

All major events, including hospitalization for COVID-19, COVID-19–related ICU care, and COVID-19–related death, were recorded until 30 June 2021. Due to uncertainties with respect to time of death and ICU care, the date of the events was interpreted as a cross-sectional event linked to the first positive COVID-19 test. Missing data for educational level and birth outside of Nordic countries were imputed by multivariate imputation by chained equations (6). Three data sets were imputed with five iterations (Supplementary Table 3) using a specified set of variables (Supplementary Table 4). Logistic regression models were performed to obtain odds ratios (ORs). The logistic regression models were analyzed on the overall cohort in order to display the odds of severe COVID-19 compared with other risk factors and further analyzed by stratifying models by the ages of <55, 55–74, and  $\geq 75$  years. The age-stratified models were analyzed with basic adjustments such as age and sex and additionally adjusted for birth outside of Nordic countries, educational level, hypertension, obesity, atrial fibrillation, venous thromboembolism (VTE), heart failure, coronary heart disease, stroke, chronic obstructive pulmonary disease (COPD), renal disease, dementia, cancer, and need of care. The overall models were adjusted for the same covariates as the fully adjusted age-stratified models. We performed sensitivity analyses among patients with type 2 diabetes stratified by insulin, oral, or no defined treatment of diabetes. Results are presented on a non-logarithmic scale to improve interpretability.

To determine the importance of coexisting conditions and socioeconomic status for the prediction of severe COVID-19, we applied two independent tree-based machine learning models, gradient boosting machines (GBMs) (7) and random forest (8), among individuals with confirmed COVID-19; the models classified individuals with type 1 and type 2 diabetes who were positive for COVID-19 to produce a model that predicted the probability of severe COVID-19 (Supplementary Fig. 3). Severe COVID-19 was defined as a

composite of hospitalization, ICU care and/or hospitalization, or death with COVID-19. Random forest is a nonlinear tree-based machine learning method where we used 500 trees for each model and tuned the number of variables randomly sampled at each split ( $n = 4-10$ ) with the R package *Caret*. GBM models were tuned via *Caret* for the number of trees ( $n = 200-1,000$ , by 200s) and interaction depth ( $n = 2, 4, 6, \text{ or } 8$ ). Parameters for minimal observation in the nodes ( $n = 10$ ) and shrinkage (0.01) were held constant. With a large class imbalance between cases and non-cases of severe COVID-19, we used the R package *DMwR* in order to balance training data using synthetic minority oversampling technique, which performed better than the original training data, and down- and upsampling classes in the training data. We trained the models with 70% of data (balanced using synthetic minority oversampling technique) with 10 cross validations (repeated three times) among individuals with type 1 diabetes and type 2 diabetes. Separate models performed and tested the two models independently against the remaining 30% (original data) for each model (see Fig. 3 for model diagnostics on test data for random forest and GBM). Original outputs from GBM and random forest on training data were independently standardized into relative importance in order to explain each feature's relative contribution to the final model (original output for each variable/summarized original output). The calculated relative importance plot figures are presented for each model by adding the GBM and random forest relative importance to each other in order to present similarities and differences between the two independent prediction models.

## RESULTS

Among the total Swedish adult population aged  $\geq 18$  years, we identified 51,402 patients with type 1 diabetes and 504,337 with type 2 diabetes, while there were 7,824,181 individuals with no registered diabetes diagnosis or diabetes medication. Patients with diabetes were less likely to have a university education, most notably among individuals with type 2 diabetes (Table 1). Among patients with type 2 diabetes aged  $< 55$  years, 39.9% were born outside a Nordic country, with corresponding proportions among the general population and the population with type 1

diabetes of 25.2% and 8.8%, respectively. Individuals with diabetes of either type had a higher prevalence of cardiovascular disease (CVD), renal disease, and COPD. Overall baseline characteristics are presented in Supplementary Table 5.

The crude absolute numbers of hospitalizations, ICU care, and death per 100,000 are presented in Fig. 1, which shows the first three waves of severe COVID-19 where rates of these outcomes increased with age, most markedly for death. We observed increased rates of these outcomes for patients with type 2 diabetes overall and regardless of age, with multiple increased rates for all outcomes compared with the general population. Individuals with type 1 diabetes only showed slightly higher rates of severe COVID-19 than the general population, although the oldest individuals (aged  $\geq 75$  years) had almost similar rates of ICU care and death as a result of COVID-19 as those with type 2 diabetes during the second wave in spring 2021, reaching rates of  $\sim 300$  deaths per 100,000 individuals in December 2020 (Fig. 1).

Total number of cases for the general population and patients with type 1 and type 2 diabetes are presented in Supplementary Table 6. The overall fully adjusted models in Supplementary Fig. 4 (adjusted for age, sex, birth outside of Nordic countries, educational level, hypertension, obesity, atrial fibrillation, VTE, heart failure, coronary heart disease, stroke, COPD, dementia, cancer, and need of care), showed that individuals with type 2 diabetes had a higher odds of all outcomes related to severe COVID-19 (hospitalization: OR 1.62 [95% CI 1.56–1.66]; ICU care: OR 1.87 [95% CI 1.78–1.96]; death: OR 1.42 [95% CI 1.37–1.48]) compared with the general population (Supplementary Fig. 4). We observed a slightly lower risk for all outcomes among individuals with no defined treatment compared with patients with type 2 diabetes taking oral glucose-lowering drugs and insulin (Supplementary Table 7). Individuals with type 1 diabetes showed slightly increased odds for hospitalization (OR 1.38 [95% CI 1.24–1.53]), while no increased odds were observed for ICU care or death compared with the general population (Supplementary Fig. 4). Markedly elevated odds were observed for all outcomes among individuals born outside of Nordic countries and for men. High education was protective for all outcomes. Several factors reflecting poor

cardiovascular and general health (having home care or living in a long-term-care facility) were associated with higher odds of death but with only slightly higher odds for ICU care, likely reflecting selective processes in the decision to provide intensive care to patients not expected to benefit.

Figure 2 shows models adjusted for age and sex and fully adjusted for the same covariates shown in Supplementary Fig. 4). Neither the basic models that were adjusted for age and sex only nor the fully adjusted models showed a statistically significant difference for individuals with type 1 diabetes for either ICU care or death for any age-group compared with the general population, although individuals aged  $< 55$  years (OR 1.59 [95% CI 1.35–1.86]) and those aged  $\geq 75$  years (OR 1.31 [95% CI 1.04–1.62]) had higher odds of hospitalization for COVID-19 compared with the general population. Individuals with type 2 diabetes, however, consistently showed statistically higher odds of all outcomes, with higher estimates for younger people compared with the general population, whereas ORs ranged from  $\sim 30-40\%$  increase in odds among the oldest individuals with type 2 diabetes to two- to threefold increased odds of severe COVID-19 in those aged  $< 55$  years in terms of hospitalization, ICU care, and death compared with the general population.

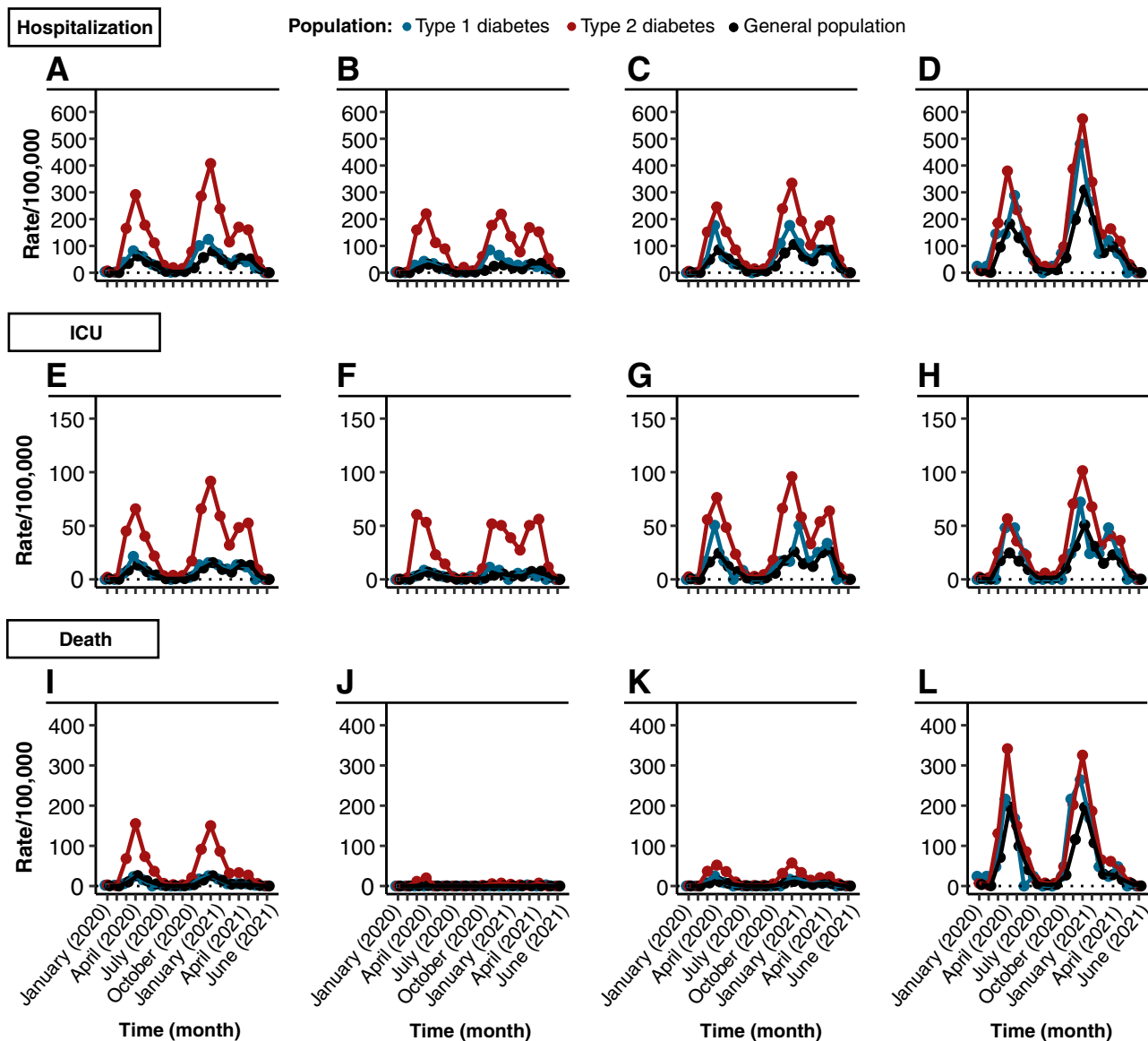
The machine learning models based on random forest and GBM showed a substantial influence of age in all models predicting severe COVID-19 for both types of diabetes and common importance of hypertension, renal disease, income level (retired), and birth place (Fig. 3). There were some marked differences in the prediction models, foremost the importance of male sex and need of care among individuals with type 2 diabetes, whereas educational level (university) was important for type 1 diabetes. In type 1 diabetes, age, hypertension, and renal disease were strong independent predictors of severe COVID-19, whereas age, social factors, and CVD were the most important in type 2 diabetes (Fig. 3). A complete list of features selected is presented in Supplementary Table 5.

## CONCLUSIONS

In this nationwide study conducted during the first three waves of COVID-19 in Sweden, we confirmed prior findings of a substantial increase in odds for the

**Table 1—Baseline characteristics among the general population and individuals with type 1 and type 2 diabetes**

	Age, years								
	General population				Type 2 diabetes				
	<55	55–74	≥75	<55	55–74	≥75	<55	55–74	≥75
Individuals, <i>n</i>	4,872,831	2,069,258	882,092	35,336	11,906	4,160	69,527	247,462	187,348
Age, mean (SD), years	36.1 (10.4)	63.9 (5.9)	81.8 (5.8)	35.7 (10.5)	63.1 (5.8)	81.5 (5.6)	45.5 (7.9)	66.0 (5.6)	81.5 (5.3)
Male sex, <i>n</i> (%)	2,502,264 (51.4)	1,003,919 (48.5)	373,478 (42.3)	19,892 (56.3)	6,496 (54.6)	1,896 (45.6)	37,608 (54.1)	151,549 (61.2)	98,836 (52.8)
Born outside of a Nordic country, <i>n</i> (%)	1,229,582 (25.2)	265,028 (12.8)	56,817 (6.4)	3,112 (8.8)	974 (8.2)	262 (6.3)	27,767 (39.9)	51,546 (20.8)	18,896 (10.1)
Education, <i>n</i> (%)									
≤9 years	733,705 (15.1)	355,915 (17.2)	327,381 (37.1)	5,166 (14.6)	2,040 (17.1)	1,513 (36.4)	15,022 (21.6)	67,543 (27.3)	81,424 (43.5)
10–12 years	2,075,611 (42.6)	969,926 (46.9)	339,628 (38.5)	16,544 (46.8)	5,855 (49.2)	1,663 (40.0)	34,415 (49.5)	121,230 (49.0)	72,938 (38.9)
University	2,063,515 (42.3)	743,417 (35.9)	215,083 (24.4)	13,626 (38.6)	4,011 (33.7)	984 (23.7)	20,090 (28.9)	58,689 (23.7)	32,986 (17.6)
Need of care, <i>n</i> (%)									
Independent living	4,853,603 (99.6)	2,033,126 (98.3)	700,473 (79.4)	35,006 (99.1)	11,521 (96.8)	3,164 (76.1)	67,873 (97.6)	234,012 (94.6)	136,494 (72.9)
Home care	6,123 (0.1)	22,800 (1.1)	116,006 (13.2)	176 (0.5)	271 (2.3)	657 (15.8)	855 (1.2)	9,697 (3.9)	34,811 (18.6)
Long-term-care facility	13,105 (0.3)	13,332 (0.6)	65,613 (7.4)	154 (0.4)	114 (1.0)	339 (8.1)	799 (1.1)	3,753 (1.5)	16,043 (8.6)
Comorbidities, <i>n</i> (%)									
Obesity (diagnosis)	100,589 (2.1)	31,817 (1.5)	9,161 (1.0)	1,062 (3.0)	360 (3.0)	101 (2.4)	10,052 (14.5)	20,250 (8.2)	9,227 (4.9)
Hypertension	37,980 (0.8)	250,460 (12.1)	342,256 (38.8)	2,202 (6.2)	3,653 (30.7)	2,602 (62.5)	10,356 (14.9)	103,290 (41.7)	122,458 (65.4)
Coronary heart disease	8,759 (0.2)	83,546 (4.0)	115,561 (13.1)	333 (0.9)	1,055 (8.9)	832 (20.0)	2,278 (3.3)	36,874 (14.9)	46,399 (24.8)
Ischemic stroke	10,881 (0.2)	45,116 (2.2)	72,760 (8.2)	253 (0.7)	522 (4.4)	532 (12.8)	1,010 (1.5)	14,430 (5.8)	24,094 (12.9)
Heart failure	5,590 (0.1)	26,061 (1.3)	67,169 (7.6)	188 (0.5)	323 (2.7)	490 (11.8)	1,097 (1.6)	13,934 (5.6)	28,826 (15.4)
Atrial fibrillation	12,442 (0.3)	65,091 (3.1)	133,496 (15.1)	136 (0.4)	494 (4.1)	854 (20.5)	848 (1.2)	18,549 (7.5)	41,688 (22.3)
VTE	37,429 (0.8)	62,166 (3.0)	57,947 (6.6)	406 (1.1)	392 (3.3)	325 (7.8)	1,742 (2.5)	11,022 (4.5)	13,676 (7.3)
COPD	15,863 (0.3)	49,339 (2.4)	56,938 (6.5)	224 (0.6)	358 (3.0)	341 (8.2)	835 (1.2)	13,327 (5.4)	16,322 (8.7)
Renal disease	12,208 (0.3)	16,458 (0.8)	21,793 (2.5)	1,243 (3.5)	827 (6.9)	299 (7.2)	1,521 (2.2)	10,679 (4.3)	13,797 (7.4)
Cancer	32,334 (0.7)	73,986 (3.6)	61,145 (6.9)	335 (0.9)	442 (3.7)	346 (8.3)	1,108 (1.6)	10,120 (4.1)	13,232 (7.1)
Dementia	1,011 (0.0)	10,257 (0.5)	44,768 (5.1)	31 (0.1)	82 (0.7)	240 (5.8)	71 (0.1)	2,422 (1.0)	10,995 (5.9)



**Figure 1**—Time trend by month (January 2020–June 2021) for COVID-19–related hospitalization, ICU care, or death among people with type 1 diabetes or type 2 diabetes and the general population. A, E, and I: Overall population. B, F, and J: Population aged <55 years at baseline. C, G, and K: Population aged 55–74 years at baseline. D, H, and L: Population aged  $\geq 75$  years at baseline.

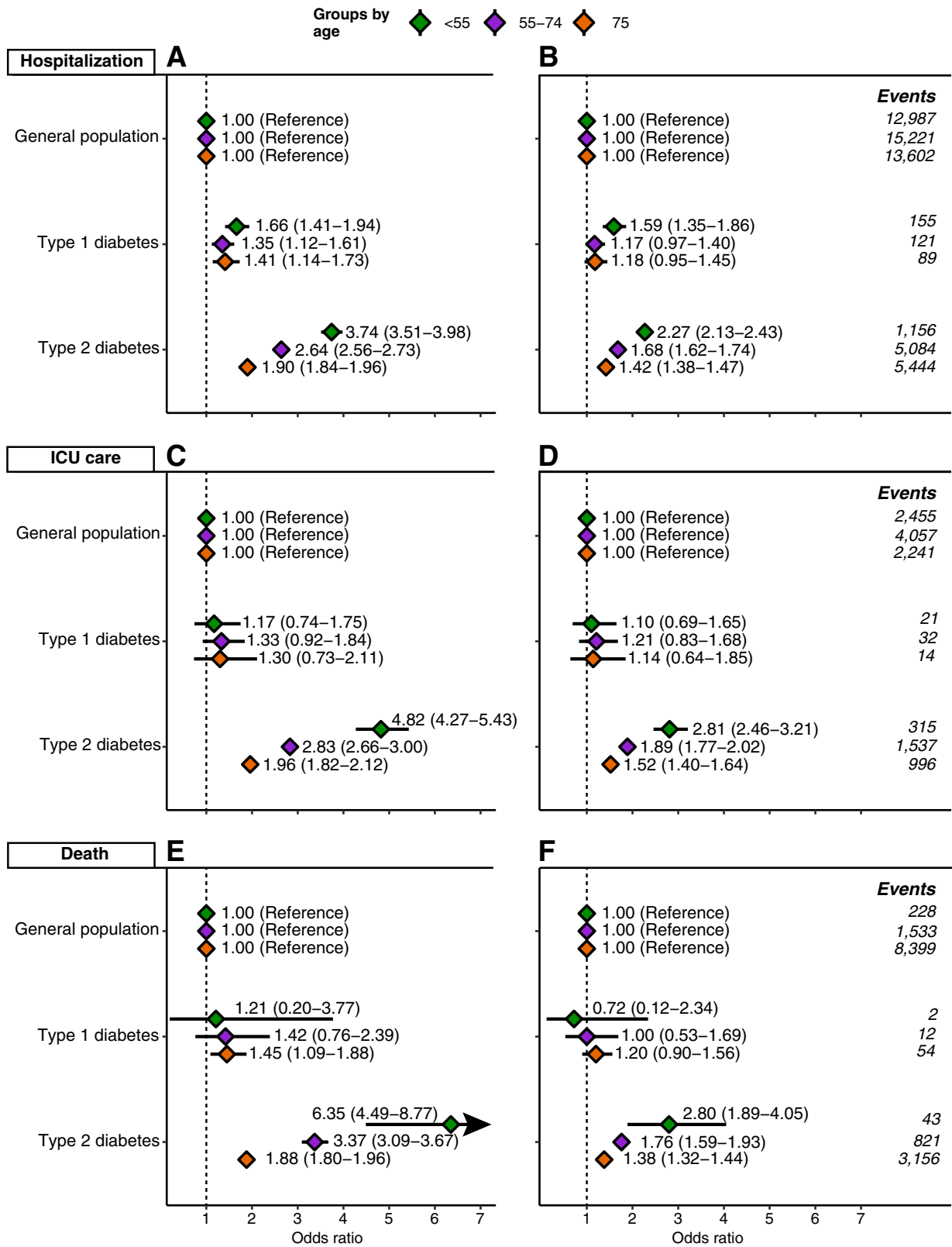
development of severe COVID-19 with respect to hospitalization, ICU care, and death among individuals with type 2 diabetes. There was a strong interaction with age, such that younger, compared with older, individuals with type 2 diabetes had considerably higher odds of an event relative to the general population without diabetes. With respect to type 1 diabetes, only a very limited number needed ICU care or died during the first three waves of COVID-19 in Sweden, with no statistically significant increased risk in ICU care or dying but with a moderately increased odds of hospitalization with COVID-19 compared with the general population. Age and

socioeconomic factors were the dominating features for predicting severe COVID-19 (hospitalization and death) in both types of diabetes.

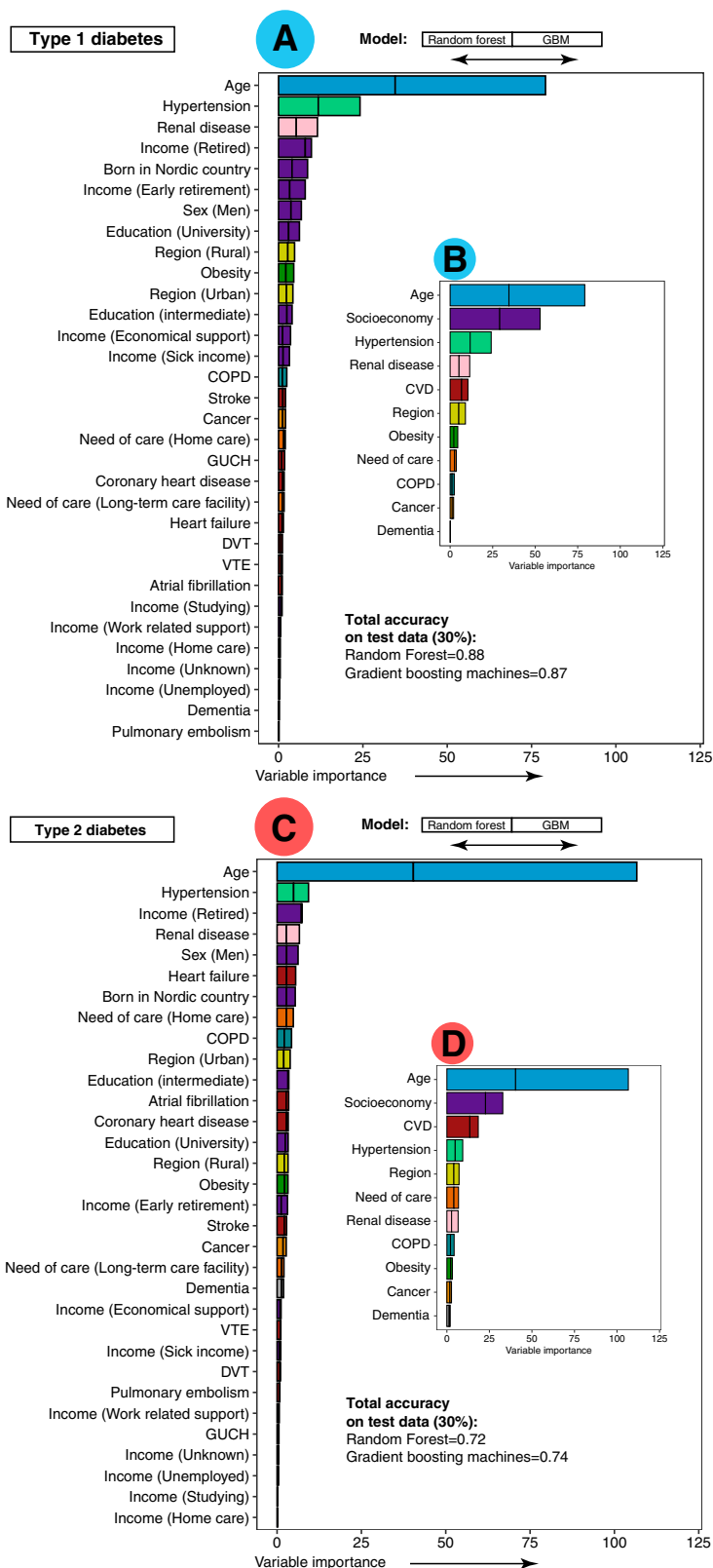
During the study period from 1 January 2020 through 30 June 2021, Sweden was subject to three waves of COVID-19. Vaccinations in Sweden began in the spring of 2021, reflecting decreased rates of ICU care and death during the third wave, particularly among elderly individuals.

The age-specific risks of type 1 and type 2 diabetes compared with a population without diabetes have been relatively unexplored. In the current study, individuals with type 2 diabetes had higher odds

of all three outcomes related to severe COVID-19 during all three waves of the pandemic, with the largest differences compared with the general population observed in people aged <55 years. This finding is partly explained by fewer competing risks in younger individuals. Given that population measures to restrict mobility may be harmful to people with type 2 diabetes (9) and that obesity has been shown to severely affect prognosis in people with COVID-19 (10), actions to reduce risk in type 2 diabetes have to be carefully balanced, with an emphasis on maintaining physical activity and avoiding weight gain and hyperglycemia (7). In the current study, a verified diagnosis of



**Figure 2**—Multiple adjusted ORs for outcomes related to severe COVID-19. Models adjusted for age and sex (left panels) and additionally for educational level, hypertension, obesity, atrial fibrillation, VTE, heart failure, coronary heart disease, stroke, COPD, renal disease, dementia, cancer, and need of care (right panels). A and B: Hospitalization. C and D: ICU care. E and F: Death. The general population is set as the reference for type 1 diabetes and type 2 diabetes.



**Figure 3**—Prediction model for severe COVID-19 among patients with type 1 diabetes and type 2 diabetes and confirmed COVID-19 infection. Models were based on random forest and GBMs. *A*: Sum of random forest and GBM importance for each separate predictor (type 1 diabetes). *B*: Sum of random forest and GBM importance by category (type 1 diabetes). *C*: Sum of random forest and GBM importance for each separate predictor (type 2 diabetes). *D*: Sum of random forest and GBM importance by category (type 2 diabetes). Variable importance indicates standardized importance as percentage of original output. DVT, deep vein thrombosis; GUCH, grownups with congenital heart defects.

obesity was not found to be a strong feature for predicting severe COVID-19, probably because of underdiagnosis of this condition (only 2.2% prevalent in this cohort). The majority of patients with type 2 diabetes are obese (11) and would have a presumed generally excess risk of death, even without any known cardiovascular risk factors (12). Hence, our findings with respect to hypertension and renal disease are relevant against the background of prior research from Sweden (4).

With respect to diabetes in general, glucose levels within control and avoidance of hyperglycemia are important for decreasing the risk of severe COVID-19 (4,13,14), where diabetes could trigger inflammatory responses, hypercoagulation, and severe pneumonia due to increased D-dimer and fibrinogen (14,15), presumably applicable also to type 1 diabetes. In 2020, patients with type 1 diabetes discharged after COVID-19 infection experienced higher risks of subsequent ICU care and death (16–18), which have been hypothesized to also be persistent in patients with well-controlled type 1 diabetes (19). However, the current study indicated no significant excess risk of ICU care or death in patients with type 1 diabetes and COVID-19, which is largely consistent with prior Swedish data (4) and other data from the U.S. (20), although our observation period was longer, allowing for a substantially larger number of outcomes than many previous studies. There were only 64 ICU admissions and 60 deaths across a whole nation with >50,000 people with type 1 diabetes, indicating a very low absolute risk of either outcome consistent with the low mean age of this group. Of the 60 deaths of patients with type 1 diabetes in the study, 48 (75%) were among those aged  $\geq 75$  years. After adjustment for comorbidities, most of which will have been secondary to presumably long-standing diabetes, there was no increase in odds. Data from the U.K. showed a substantially increased mortality risk among individuals with type 1 diabetes in the early months of the pandemic (3). The Swedish health care system is aimed toward an equal access to health care for everyone, where, for example, insulin comes free of charge. In addition, the Swedish National Diabetes Register, a quality register with high coverage that registers relevant data on treatment, complications, and risk factors annually



with an aim to improve national diabetes care (21), may have resulted in a population with relatively well controlled type 1 diabetes (22). Accordingly, the study would indicate that at least younger and middle-aged individuals with type 1 diabetes, particularly if uncomplicated, are not at any risk of needing ICU care or death over and above that of their contemporary peers without diabetes.

With respect to hospitalization for COVID-19 in type 1 diabetes, there was a significant independent increase in odds of hospitalization for COVID-19 as opposed to ICU care and death. In a U.S. study, the risk for hospitalization conferred by COVID-19 was approximately four times higher compared with individuals without type 1 diabetes (20). Against the background of the recommendations issued for patients with diabetes and COVID-19 (23), reasons for the increased hospitalization rate may be a higher propensity of admitting patients with type 1 diabetes because of higher perceived risk. In patients with type 1 diabetes, even though physical hospital visits may have decreased, evidence suggests the possibility that their glycemic control was not greatly affected by the ongoing pandemic (24). Another possibility for the observed low odds of hospitalization and death is that patients with type 1 diabetes may have taken precautionary measures, including working from home to a greater extent than those without diabetes, although no Swedish recommendations targeted type 1 diabetes specifically. Of note, the Swedish recommendations were not forced restrictions, except for organized events. However, like previous Swedish data with shorter follow-up time (4), tendencies of increased ICU care and death were observed in patients with type 1 diabetes in the overall analyses, and age-specific odds could be low because of lack of power, which should be considered as an explaining factor.

The prediction models for severe COVID-19 among individuals with type 1 diabetes and confirmed infection found that socioeconomic status had an almost equal impact as age for the prediction of severe COVID-19, where educational level was highlighted. Although the Swedish health care system in theory would guarantee the same level of care to all citizens, previous research has shown that socioeconomic status could influence both risk factor level (25) and late complications (26); thus, the aspect of socioeconomic

status and severe COVID-19 should probably be taken into consideration in future prevention of severe COVID-19 in patients with type 1 diabetes.

Strengths of the study were the large population sample, including a majority of the Swedish adult population with ~500,000 adults with type 2 diabetes and ~50,000 adults with type 1 diabetes identified by the Swedish Patient Register, and that we were able to identify virtually all hospital diagnoses since 1987 and out-of-hospital visits from 2001 and onward. We were also able to identify patients with type 2 diabetes treated in primary care only through the Swedish Prescribed Drug Register. The Swedish Patient Register, the Intensive Care Register, and the Cause of Death Register provided nearly complete coverage of events concerning COVID-19.

The study had some limitations. First, data were lacking on anthropometric measures, smoking, and metabolic control, which have previously been shown to be important (4,13). Second, testing capacity was limited during the first wave of pandemic, although diabetes has not been associated with an increased risk of being infected with the virus (27). With the Swedish personal identification number (28) and virtually all registered in-hospital stays since 1987 (29), out-of-hospital visits since 2001, and data from the Swedish Prescribed Drug Register, we likely captured the absolute majority of all individuals with diabetes of either type in Sweden during the Alpha to Delta variations of the virus during the entire prevaccination phase. Finally, the limited number of events among the comparatively young patients with type 1 diabetes, coupled with the low absolute risk of adverse outcomes in younger people, should also be considered when interpreting our findings.

In conclusion, we confirm that type 2 diabetes confers an excess risk of severe COVID-19 compared with the general population while adding that the highest odds of an event related to hospitalization, ICU care, and death were found in people aged <55 years but where the difference decreased with older age. Among patients with type 1 diabetes, we found similar odds of a severe event (ICU care and death) related to COVID-19 in any age-group, with the exception of hospitalization in younger individuals. In individuals with type 1 diabetes and type 2 diabetes with COVID-19 infection alike, age was the dominating predictor of severe COVID-19,

whereas socioeconomic status may be an important feature in the risk assessment among all individuals with diabetes.

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## References

1. COVID-19 Excess Mortality Collaborators. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. *Lancet* 2022;399:1513-1536
2. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020;8:782-792
3. Barron E, Bakhai C, Kar P, 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;8:813-822
4. Rawshani A, Kjölhede EA, Rawshani A, et al. Severe COVID-19 in people with type 1 and type 2 diabetes in Sweden: a nationwide retrospective cohort study. *Lancet Reg Health Eur* 2021;4:100105
5. Demirci I, Haymana C, Tasci I, et al. Higher rate of COVID-19 mortality in patients with type 1 than type 2 diabetes: a nationwide study. *Endokrynol Pol* 2022;73:87-95
6. Azur MJ, Stuart EA, Frangakis C, Leaf PJ. Multiple imputation by chained equations: what is it and how does it work? *Int J Methods Psychiatr Res* 2011;20:40-49
7. Elith J, Leathwick JR, Hastie T. A working guide to boosted regression trees. *J Anim Ecol* 2008;77:802-813
8. Breiman L. Random forests. *Mach Learn* 2001;45:5-32
9. Sutkowska E, Marciniak DM, Sutkowska K, Biernat K, Mazurek J, Kuciel N. The impact of lockdown caused by the COVID-19 pandemic on glycemic control in patients with diabetes. *Endocrine* 2022;76:273-281
10. Gao M, Piernas C, Astbury NM, et al. Associations between body-mass index and COVID-19 severity in 6.9 million people in England: a

- prospective, community-based, cohort study. *Lancet Diabetes Endocrinol* 2021;9:350–359
11. Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med* 2015;373:1720–1732
12. Rawshani A, Rawshani A, Franzén S, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;379:633–644
13. Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020;8:823–833
14. Sardu C, D’Onofrio N, Balestrieri ML, et al. Outcomes in patients with hyperglycemia affected by COVID-19: can we do more on glycemic control? *Diabetes Care* 2020;43:1408–1415
15. Guo W, Li M, Dong Y, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020;36:e3319
16. Barrett CE, Park J, Kompaniyets L, et al. Intensive care unit admission, mechanical ventilation, and mortality among patients with type 1 diabetes hospitalized for COVID-19 in the U.S. *Diabetes Care* 2021;44:1788–1796
17. McGurnaghan SJ, Weir A, Bishop J, et al.; Public Health Scotland COVID-19 Health Protection Study Group; Scottish Diabetes Research Network Epidemiology Group. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. *Lancet Diabetes Endocrinol* 2021;9:82–93
18. Gregory JM, Slaughter JC, Duffus SH, et al. COVID-19 severity is tripled in the diabetes community: a prospective analysis of the pandemic’s impact in type 1 and type 2 diabetes. *Diabetes Care* 2021;44:526–532
19. Gregory JM, Moore DJ. The dual burden of type 1 diabetes and COVID-19. *Ann Intern Med* 2021;174:703–704
20. Demeterco-Berggren C, Ebekozien O, Rompicherla S, et al. Age and hospitalization risk in people with type 1 diabetes and COVID-19: data from the T1D Exchange Surveillance Study. *J Clin Endocrinol Metab* 2022;107:410–418
21. Eliasson B, Gudbjörnsdóttir S. Diabetes care—improvement through measurement. *Diabetes Res Clin Pract* 2014;106(Suppl. 2):S291–S294
22. Albanese-O’Neill A, Grimsman JM, Svensson AM, et al. Changes in HbA1c between 2011 and 2017 in Germany/Austria, Sweden, and the United States: a lifespan perspective. *Diabetes Technol Ther* 2022;24:32–41
23. Papadokostaki E, Tentolouris N, Liberopoulos E. COVID-19 and diabetes: what does the clinician need to know? *Prim Care Diabetes* 2020;14:558–563
24. Patel SY, McCoy RG, Barnett ML, Shah ND, Mehrotra A. Diabetes care and glycemic control during the COVID-19 pandemic in the United States. *JAMA Intern Med* 2021;181:1412–1414
25. Edqvist J, Rawshani A, Rawshani A, et al. Trajectories in HbA1c and other risk factors among adults with type 1 diabetes by age at onset. *BMJ Open Diabetes Res Care* 2021;9: e002187
26. Rawshani A, Svensson AM, Rosengren A, Eliasson B, Gudbjörnsdóttir S. Impact of socioeconomic status on cardiovascular disease and mortality in 24,947 individuals with type 1 diabetes. *Diabetes Care* 2015;38:1518–1527
27. Rosengren A, Lundberg CE, Söderberg M, et al. Severe COVID-19 in people 55 and older during the first year of the pandemic in Sweden. *J Intern Med* 2022;292:641–653
28. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekblom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;24:659–667
29. Ludvigsson JF, Andersson E, Ekblom A, et al. External review and validation of the Swedish National Inpatient Register. *BMC Public Health* 2011;11:450