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Risk of Severe Coronavirus Disease 2019 Disease in Individuals With Down Syndrome: A Matched Cohort Study From a Large, Integrated Health Care System

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(See the Editorial Commentary by Atkinson, on pages 755–6.)

Background. Down syndrome (DS) is associated with an increased risk of infections attributed to immune defects. Whether individuals with DS are at an increased risk of severe coronavirus disease 2019 (COVID-19) remains unclear.

Methods. In a matched cohort study, we evaluated the risk of COVID-19 infection and severe COVID-19 disease in individuals with DS and their matched counterparts in a pre-COVID-19 vaccination period at Kaiser Permanente Southern California. Multivariable Cox proportion hazard regression was used to investigate associations between DS and risk of COVID-19 infection and severe COVID-19 disease.

Results. Our cohort included 2541 individuals with DS and 10 164 without DS matched on age, sex, and race/ethnicity (51.6% female, 53.3% Hispanic, median age 25 years [interquartile range, 14–38]). Although the rate of COVID-19 infection in individuals with DS was 32% lower than their matched counterparts (adjusted hazard ratio [aHR], 0.68; 95% confidence interval [CI], .56–.83), the rate of severe COVID-19 disease was 6-fold higher (aHR, 6.14; 95% CI, 1.87–20.16).

Conclusions. Although the risk of COVID-19 infection is lower, the risk of severe disease is higher in individuals with DS compared with their matched counterparts. Better infection monitoring, early treatment, and promotion of vaccine for COVID-19 are warranted for DS populations.

Keywords. COVID-19; COVID-19 death; COVID-19 hospitalization; down syndrome.

Down syndrome (DS) is a genetic disorder caused by abnormalities involving chromosome 21, most often due to the presence of an extra copy of this chromosome (complete trisomy 21) [1]. Other causes of DS include mosaic trisomy 21 and translocation trisomy 21 [2]. Down syndrome is the most common chromosomal disorder in the United States (U.S.). Each year, approximately 6000 babies are born with DS in the U.S., which is approximately 1 in every 700 newborns [3]. Between 1979 and 2003, the prevalence of DS at birth per 10 000 live births increased by 31.1%, from 9.0 to 11.8 in 10 U.S. regions [4]. In 2010, an estimated total of 206 366 individuals (6.7 per 10 000) were living with DS in the U.S. [5].

Down syndrome is also the most common congenital cause of mental disability, and is often accompanied by metabolic and structural adverse health events [1–6]. For example, individuals with DS commonly experience congenital and subsequently acquired cardiac, pulmonary, intellectual, neurologic, and gastrointestinal abnormalities [2]. More importantly, individuals with DS have an increased risk of infections, especially pulmonary infections. These are attributed to immune defects, such as T and B cell lymphopenia with decreased naive lymphocytes, impaired mitogen-induced T cell proliferation, and reduced specific antibody responses to immunizations [7–13]. Other important abnormalities include the absence of normal lymphocyte expansion in infancy, decreased immunoglobulin A in saliva, and decreased neutrophil chemotaxis [2, 14–17]. Immune deficits may result in suboptimal immune responses to vaccinations. Furthermore, the transmembrane serine protease (TMPRSS2) is encoded within chromosome 21, which is essential for viral attachment and entry into cells in other coronaviruses [9]. It is suggested that overexpression of TMPRSS2 may increase efficiency of infection, thereby increasing susceptibility to coronavirus disease 2019 (COVID-19) in individuals with DS [9].

Since the COVID-19 pandemic began in March 2020, several non-U.S. studies have reported on an increased risk of COVID-19 infection and more severe outcomes in individuals with DS compared to those without [18–20]. A report from New York City documented more severe COVID-19 disease

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in hospitalized DS individuals compared to matched counterparts without DS [21]. These studies suggested the need for enhanced monitoring and specialized care for people with DS.

Down syndrome is listed by the U.S. Centers for Disease Control and Prevention (CDC) among the comorbidities associated with severe COVID-19 [22]. Current evidence suggests that DS may be a relevant risk factor for severe COVID-19 [3, 18–20]. However, we lack population-based studies to quantify the incidence of COVID-19 infection and risk of severe COVID-19-related outcomes in a large DS population, especially in the U.S. Therefore, in the pre-COVID-19 vaccination period, we examined COVID-19 infection and severe COVID-19 disease in a large cohort of individuals with DS compared to matched counterparts without DS at Kaiser Permanente Southern California (KPSC).

METHODS

Study Setting and Population

We used electronic health records (EHRs) data at KPSC. KPSC is an integrated healthcare system that provides prepaid comprehensive healthcare to more than 4.6 million members in Southern California. KPSC's EHRs include data on demographics, healthcare utilization (outpatient/inpatient encounters and emergency department), diagnoses, laboratory tests, pharmacy usage, vaccination, membership history, and mortality. The demographic composition at KPSC is representative of the Southern California population [23, 24]. Compared to the racial/ethnic distribution of the U.S., KPSC membership is composed of twice as many Asian members and 3 times as many Hispanic members [25].

Study Design

This was a matched cohort study to assess whether individuals with DS were at an increased risk of COVID-19 infection and developing severe COVID-19 disease compared to those without DS. Because our intention was to examine natural disease risk, the study period was between March 1, 2020 and December 31, 2020, before the wide distribution of COVID-19 vaccines. Individuals were censored at the time of COVID-19 vaccination if received before December 31, 2020. The exposure of interest was a diagnosis of DS, identified *by International Classification of Diseases* (ICD) *9th* and *10th Revision*, *Clinical Modification* (CM) codes (ICD-9-CM 758.0 and ICD-10-CM Q90.0) before the study start date (March 1, 2020).

Individuals with DS were matched in a 1:4 ratio with individuals without DS by age, sex (female, male), and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian, and other/unknown). We included individuals of all ages with at least 1 year of continuous KPSC membership before the study start date, allowing for a 31-day gap. The baseline period was defined as the 12-month period before the study start date. Individuals with DS and their matched counterparts were observed from the study start date until (1) development of the outcomes of interest, (2) discontinuation of KPSC membership, (3) death, (4) receipt of any dose of COVID-19 vaccine, or (5) end of study period (December 31, 2020), whichever came first. This study was approved by the KPSC Institutional Review Board with a waiver of informed consent.

Outcome of Interest and Covariates

The primary outcomes of interest were as follows: (1) COVID-19 infection; (2) severe COVID-19 disease; and (3) COVID-19 hospitalization death. Coronavirus disease 2019 infection was defined as patients' first positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) molecular test or COVID-19 diagnosis code. Severe COVID-19 disease was defined as COVID-19 hospitalization (hospitalization with a SARS-CoV-2 positive test or a COVID-19 diagnosis, or a hospitalization occurring within 7 days after a SARS-CoV-2 positive test) and COVID-19 hospitalization death. Coronavirus disease 2019 hospitalization death was defined as death during a COVID-19 hospitalization.

Secondary outcomes included the following: (1) 31-day COVID-19 mortality, defined as death occurring within 31 days of the first COVID-19 diagnosis; (2) intensive care unit admission during the first COVID-19 hospitalization; (3) use of invasive mechanical ventilation during the first COVID-19 hospitalization; (4) length of COVID-19 hospitalization, defined as the number of days in hospital during the first COVID-19 hospitalization; and (5) 31-day post-COVID-19 hospitalization mortality, defined as death occurring within 31 days after discharge date.

Baseline patients/clinical characteristics examined were: age at study start, sex, race/ethnicity, body mass index (BMI), smoking history, healthcare utilization (number of outpatient/emergency department visits and number of hospitalizations), frailty index [26], baseline comorbidities, and primary medical center area as a proxy for geographic location. Baseline characteristics that could be potential confounders were selected a priori and were identified by ICD-9-CM or ICD-10-CM codes documented during the baseline period. Selected potential confounders included BMI, smoking status, healthcare utilizations, frailty index, baseline comorbidities, and medical center. Those with a confirmed COVID-19 diagnosis before study start date (March 1, 2020) were excluded.

Statistical Analysis

We calculated absolute standardized differences and *P* values to assess the balance of covariates and to determine potential confounders. We examined the associations between DS and the following: (1) COVID-19 infection; (2) severe COVID-19

disease; and (3) COVID-19 hospitalization death. Incidence rates (IRs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were generated to compare outcomes in individuals with and without DS. We used Cox proportion hazard model to estimate HRs comparing COVID-19 infection and severe COVID-19 disease in individuals with and without DS, while adjusting for potential confounders (BMI, smoking, number of outpatient visits, number of emergency department visits, number of hospitalizations, frailty status based on frailty index, all baseline comorbidities, and medical center area). Kaplan-Meier curves were used to estimate the cumulative incidence during the study period. Model assumptions were assessed by proportionality test.

RESULTS

Our cohort included 2541 individuals with DS and 10 164 individuals without DS matched on age, sex, and race/ethnicity (Table 1). The cohort had a slightly higher proportion of females (51.6%) than males, more Hispanic individuals (53.3%) than other racial/ethnic groups, and a median age of 25 years (interquartile range [IQR], 14–38 years). Overall, individuals with DS had a higher BMI and more frequent outpatient and emergency department visits and hospitalizations than matched counterparts without DS during 12 months before the study start date. More individuals with DS were frail (top quartile of frailty index), but fewer individuals reported a history of smoking compared to individuals without DS. Most baseline comorbidities, including pulmonary disease, diabetes, autoimmune disease, cardiovascular disease, renal disease, and cancer, were more common in individuals with DS compared to their matched counterparts.

During follow-up, COVID-19 infection occurred in 142 of 2541 individuals with DS (IR = 68.58 per 1000 person-years; 95% CI, 58.18–80.84) and in 695 of 19 164 matched counterparts without DS (IR = 86.21 per 1000 person-years; 95% CI, 80.04–92.87) (Table 2). Severe COVID-19 disease was more common in those with DS (IR = 12.46; 95% CI, 8.48–18.29) than matched counterparts (IR = 3.06; 95% CI, 2.07–4.52). Incidence rates for COVID-19 hospitalization death were also higher for individuals with DS (IR = 2.39; 95% CI, .99–5.74) compared to matched counterparts (IR = 0.12; 95% CI, .02–.87). The adjusted HR of COVID-19 infection comparing individuals with DS and matched counterparts was 0.68 (95% CI, .56–.83), which indicates that the DS population had a 32% lower risk of COVID-19 infection. The incidence of severe COVID-19 disease was increased by more than 6-fold in individuals with DS compared to matched counterparts (HR = 6.14; 95% CI, 1.87–20.16). Five COVID-19 hospital deaths occurred in patients with DS, whereas 1 occurred in non-DS counterparts (unadjusted HR = 18.20; 95% CI, 2.11–156.86; adjusted HR not estimated due to lack of model convergence).

The Kaplan-Meier plot for cumulative incidence estimates of COVID-19 infection by DS status demonstrated similar cumulative incidence estimates for individuals with and without DS when infection rate in the community was still low at the beginning of the pandemic (Figure 1). However, the plot demonstrated an infection rate increase in July 2020 (at 4 months of observation), and in November 2020 (at 8 months of observation), after which the cumulative incidence for individuals with DS was consistently higher than for their counterparts. Figures 2 and 3 show consistently higher cumulative incidence estimates of COVID-19 hospitalization and COVID-19 hospitalization deaths for individuals with DS compared to those without DS.

Other severe COVID-19 outcomes were also more common in individuals with DS compared to the matched counterparts (Table 3). Seven (0.3%) individuals with DS died within 31 days of COVID-19 infection, while none died in the matched counterparts. The median length of first COVID-19 hospitalization was 6.5 days (IQR, 5–11; range 1–59) for individuals with DS, while median length was 5.0 days (IQR, 4–10; range 2–76) for the matched counterparts. Intensive care unit admission was also more common in individuals with DS ($n = 6$, 0.23%) than matched counterparts ($n = 3$, 0.03%).

DISCUSSION

In this study, we examined the incidence of COVID-19 infection, severe COVID-19 disease, and COVID-19 hospitalization death in individuals with DS in the pre-COVID-19 vaccination period between March 1, 2020 and December 31, 2020 at KPSC. Our results showed that the risk of COVID-19 infection was lower in individuals with DS compared to matched counterparts. Individual protective behaviors against COVID-19 likely vary between individuals with and without DS, and these differences are very difficult to measure. Caregivers of individuals with DS may promote more COVID-19 precautions, including isolation, than those without DS, which may result in a lower incidence of COVID-19 infection in those with DS. However, our results showed that the risks of severe COVID-19 disease and COVID-19 hospital death were higher in individuals with DS compared to those without DS. Other indicators of severe COVID-19 outcome, including intensive care unit admission, were also longer and more common in hospitalized COVID-19 patients with DS than those without.

Several studies have evaluated the risk of COVID-19 infection and associated outcomes in DS population, but these have been limited by small sample size. A description of the clinical course in 4 COVID-19 patients with DS in Belgium revealed severe illness in 3 of 4 cases, with fatal outcome in 1 patient [18]. In a dual-center study of patients hospitalized with COVID-19 in New York City, researchers reported an increased COVID-19 severity in 12 hospitalized patients with

Table 1. Baseline Characteristics of 2541 Individuals With Down Syndrome and 10 164 Matched Counterparts Without Down Syndrome at Kaiser Permanente Southern California, March 1, 2020–December 31, 2020

Characteristics	DS (N = 2541)	non-DS (N = 10 164)	Total (N = 12 705)	Absolute Standard Difference
Age at Index Date, Years, *n* (%)				N/A[c]
<18	1420 (55.9)	5680 (55.9)	7100 (55.9)	
18–49	851 (33.5)	3404 (33.5)	4255 (33.5)	
≥50	270 (10.6)	1080 (10.6)	1350 (10.6)	
Mean (s.d.)	27.1 (16.0)	27.1 (16.0)	27.08 (16.0)	
Median (quartile 1st, 3rd)	25 (14, 38)	25 (14, 38)	25 (14, 38)	
Sex, *n* (%)				N/A[c]
Female	1312 (51.6)	5248 (51.6)	6560 (51.6)	
Male	1229 (48.4)	4916 (48.4)	6145 (48.4)	
Race/Ethnicity, *n* (%)				N/A[c]
Hispanic	1354 (53.3)	5416 (53.3)	6770 (53.3)	
Non-Hispanic White	744 (29.3)	2976 (29.3)	3720 (29.3)	
Non-Hispanic Black	192 (7.6)	768 (7.6)	960 (7.6)	
Non-Hispanic Asian	183 (7.2)	732 (7.2)	915 (7.2)	
Other/unknown	68 (2.7)	272 (2.7)	340 (2.7)	
Body mass index[a], *n* (%)				0.4203
<18.5	309 (12.2)	1334 (13.1)	1643 (12.9)	
18.5 to <25	585 (23.0)	2409 (23.7)	2994 (23.6)	
25 to <30	490 (19.3)	1902 (18.7)	2392 (18.8)	
30 to <35	387 (15.2)	1081 (10.6)	1468 (11.6)	
35 to <40	265 (10.4)	588 (5.8)	853 (6.7)	
40 to <45	107 (4.2)	271 (2.7)	378 (3.0)	
≥45	109 (4.3)	145 (1.4)	254 (2.0)	
Unknown	289 (11.4)	2434 (23.9)	2723 (21.4)	
Smoking[b], *n* (%)				0.3858
No	2177 (85.7)	7156 (70.4)	9333 (73.5)	
Yes	68 (2.7)	834 (8.2)	902 (7.1)	
Unknown	296 (11.6)	2174 (21.4)	2470 (19.4)	
Number of Outpatient Visits[b], *n* (%)				0.6700
0	160 (6.3)	1802 (17.7)	1962 (15.4)	
1–4	802 (31.6)	4990 (49.1)	5792 (45.6)	
5–10	746 (29.4)	2147 (21.1)	2893 (22.8)	
≥11	833 (32.8)	1225 (12.1)	2058 (16.2)	
Number of Emergency Department Visits[b], *n* (%)				0.1458
0	2081 (81.9)	8790 (86.5)	10 871 (85.6)	
1	310 (12.2)	1043 (10.3)	1353 (10.6)	
≥2	150 (5.9)	331 (3.3)	481 (3.8)	
Number of Hospitalizations[b], *n* (%)				0.1061
0	2428 (95.6)	9890 (97.3)	12 318 (97.0)	
1	88 (3.5)	242 (2.4)	330 (2.6)	
≥2	25 (1.0)	32 (0.3)	57 (0.4)	
Frailty Index[b], *n* (%)				0.2871
No	1644 (64.7)	7885 (77.6)	9529 (75.0)	
Yes (top quartile)	897 (35.3)	2279 (22.4)	3176 (25.0)	
Baseline Comorbidities[b], *n* (%)				
Pulmonary disease	332 (13.1)	848 (8.3)	1180 (9.3)	0.1532
Diabetes	138 (5.4)	341 (3.4)	479 (3.8)	0.1014
Hypertension	108 (4.3)	543 (5.3)	651 (5.1)	0.0511
Autoimmune diseases	102 (4.0)	108 (1.1)	210 (1.7)	0.1885
Cardiovascular disease	94 (3.7)	117 (1.2)	211 (1.7)	0.1662
Renal disease	76 (3.0)	74 (0.7)	150 (1.2)	0.1681
Cancer	35 (1.4)	57 (0.6)	92 (0.7)	0.0834
Human immunodeficiency virus	0 (0.0)	18 (0.2)	18 (0.1)	0.0596

Abbreviations: DS, Down syndrome; N/A, not applicable; non-DS, matched counterparts without Down syndrome; s.d., standard deviation.

[a]Most recent in 365 days before March 1, 2020.

[b]In 365 days before March 1, 2020.

[c]N/A for matching variable.

Table 2. Incidence Rates and Hazard Ratios of COVID-19 Infection, Severe COVID-19 Disease, and COVID-19 Hospitalization Death Among 2541 Individuals With Down Syndrome and 10 164 Matched Counterparts Without Down Syndrome at Kaiser Permanente Southern California, March 1, 2020 to December 31, 2020

	DS			non-DS			Hazard Ratio (95% CI)	
Primary Outcome	N	Number of Cases	Incidence per 1000 Person-Years (95% CI)	N	Number of Cases	Incidence per 1000 Person-Years (95% CI)	Unadjusted	Adjusted[a]
COVID-19 infection	2541	142	68.58 (58.18–80.84)	10 164	695	86.21 (80.04–92.87)	0.76 (.64–.92)	0.68 (.56–.83)
Severe COVID-19 disease	2541	26	12.46 (8.48–18.29)	10 164	25	3.06 (2.07–4.52)	4.17 (2.37–7.32)	6.14 (1.87–20.16)
COVID-19 hospitalization death	2541	5	2.39 (.99–5.74)	10 164	1	0.12 (.02–.87)	18.20 (2.11–156.86)	N/A

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; DS, Down syndrome; N/A, not applicable; non-DS, matched counterparts without Down syndrome.

[a]Adjusted for covariates: body mass index, smoking, number of outpatient visits, number of emergency department visits, number of hospitalizations, frailty status based on frailty index (yes/no), all baseline comorbidities, and medical center area.

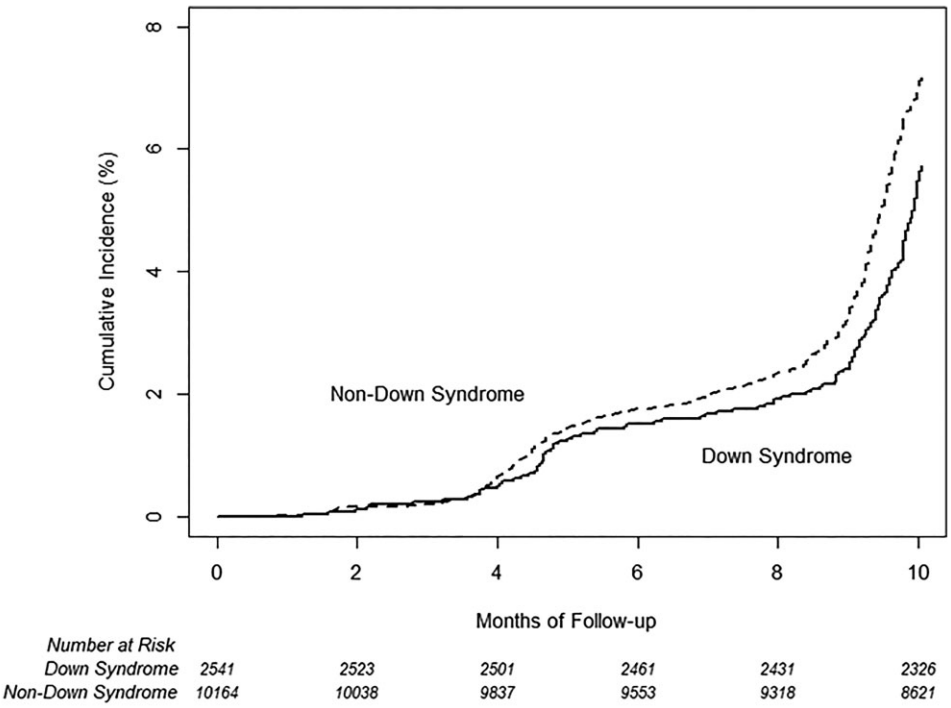

Figure 1. Cumulative incidence estimates of coronavirus disease 2019 infection by Down syndrome status, Kaiser Permanente Southern California, March 1, 2020–December 31, 2020.

DS compared to age-matched patients without DS. In this study, among patients hospitalized with COVID-19, patients with DS had more COVID-19-related complications, including acute respiratory distress syndrome, sepsis, and requiring mechanical ventilator compared to their matched non-DS counterparts [21]. A study in England examined DS as a risk factor for COVID-19 death using a large population-level primary care database, and estimated a 4-fold increase in the risk for COVID-19-related hospitalization and a 10-fold increase in the risk for COVID-19-related death compared to those without DS [20]. More recently, Illouz et al [19], using global catalogs of surveys, censuses, vital statistics, and other health-related data, reported a significant correlation between COVID-19-related deaths (normalized to 1 million in every country) and the prevalence of DS per country. Our results from large, population-based data, demonstrating an increased risk of severe COVID-19 disease in DS individuals compared to their matched counterparts without DS, confirm the existing literature.

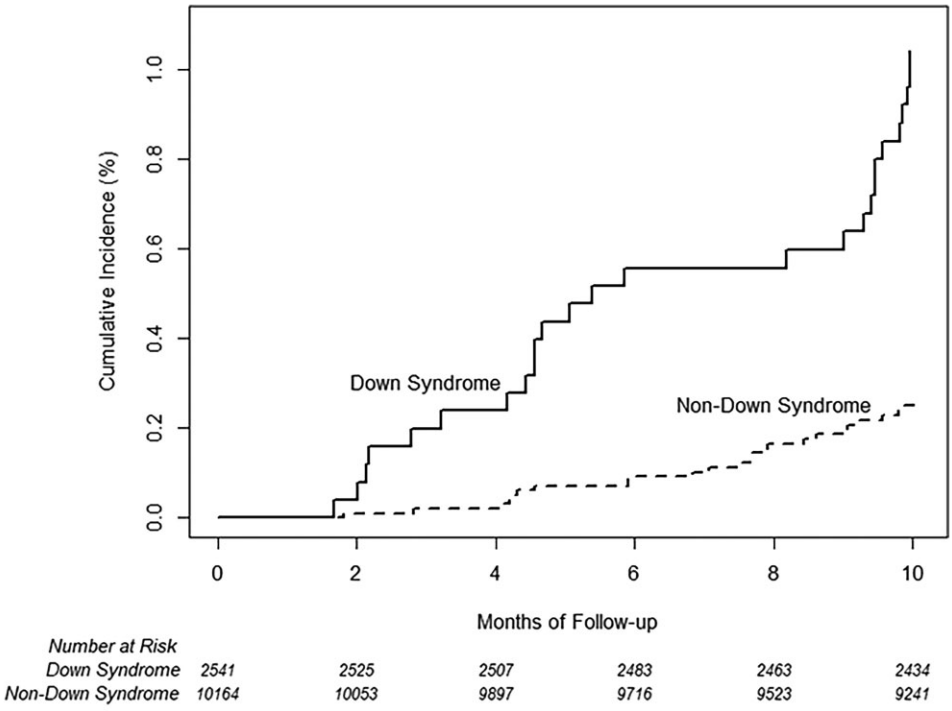

Figure 2. Cumulative incidence estimates of coronavirus disease 2019 hospitalization by Down syndrome status, Kaiser Permanente Southern California, March 1, 2020–December 31, 2020.

Several physiologic and immunologic factors related to DS may explain the increased risk of severe COVID-19 disease in DS populations. The immune dysregulation caused by trisomy 21 is thought to result in an exacerbated cytokine release syndrome relative to that observed in the euploid population [3]. Dysregulation and increased cytokine production in individuals with DS may increase the severity of their COVID-19 disease, because mortality is mainly related to cytokine release syndrome [18]. Mild to severe cytokine storm is characteristic of severe COVID-19 disease, often leading to death [27]. Some studies also have shown elevated interleukin-6 concentrations in patients with DS compared to those without DS, which may indicate that such patients have higher levels of inflammatory markers [21]. However, whether increased inflammatory markers detected in DS alter the response to COVID infection or are part of the mechanism that determines disease severity is not yet established. In addition, in our cohort, among comorbidities that may be associated with susceptibility to COVID-19, including diabetes, pulmonary disease, and renal disease, all were more common in DS patients than in matched counterparts. In fact, airway obstruction, pulmonary hypertension, and congenital heart disease have been reported in DS patients hospitalized with COVID-19 [28]. Furthermore, previous reports have shown that chronic lung disease was significantly more common in COVID-19 patients with DS than those without DS, and that the risk for COVID-19 infection was further elevated in those with chronic lung disease [19]. Although we adjusted for potential confounders, there could still be residual confounding and other important attributes associated with DS that contribute to the increased risk of severe COVID disease. The association between such comorbidities and increased susceptibility to severe COVID-19 outcomes needs further investigation.

Although we did not observe an increased risk of COVID-19 infection in individuals with DS, we observed an increase in the risk of severe COVID-19 outcomes compared to matched counterparts. COVID-19 patients with DS may be more likely to be hospitalized as a precautionary measure compared to those without DS due to other underlying conditions common in DS; this could potentially result in an overestimation of the COVID-19 hospitalization risk. However, indicators of severe COVID-19 outcomes including mortality and use of invasive ventilation, which are unlikely influenced by behavior factors, consistently demonstrated a higher risk of severe COVID-19 outcomes in those with DS.

This study has several strengths. U.S. data on the risk of COVID-19 infection and severe outcomes in individuals with DS are very limited. Our study adds important population-based, real-world data on COVID-19 infection and severe COVID-19 outcomes in individuals with DS. The study made

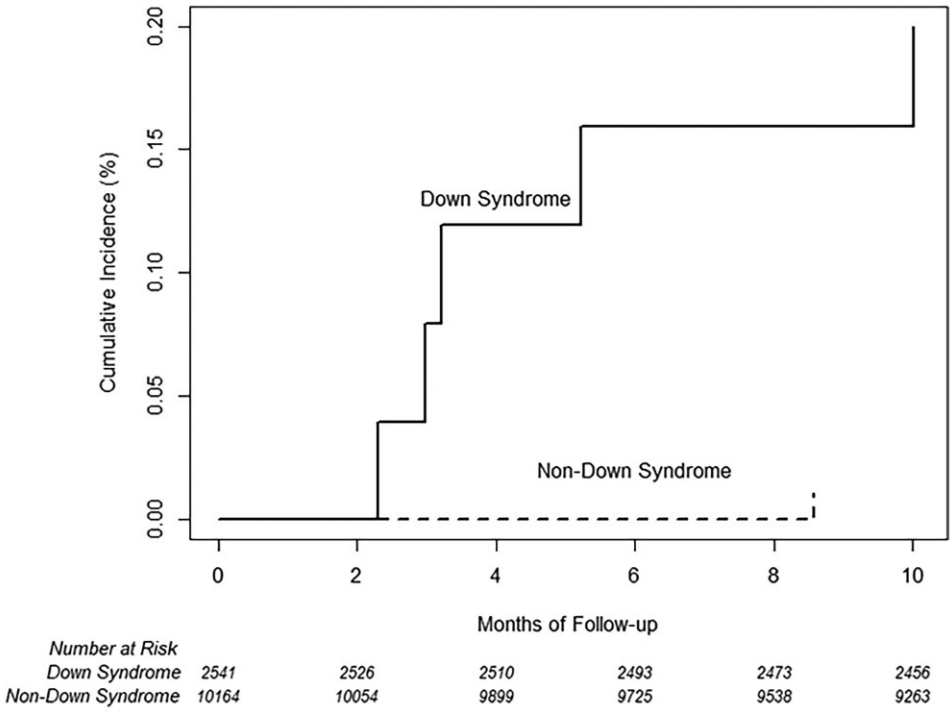

Figure 3. Cumulative incidence estimates of coronavirus disease 2019 hospitalization death by Down syndrome status, Kaiser Permanente Southern California, March 1, 2020–December 31, 2020.

Table 3. Secondary Outcomes (Other Severe COVID-19 Outcomes) by Down Syndrome Status, Kaiser Permanente Southern California, March 1, 2020–December 31, 2020

Severe COVID-19 Outcomes	Down Syndrome (N = 2541)	Matched Counterparts (N = 10 164)
31-day COVID-19 mortality, *n* (%)	7 (0.3)	0 (0.0)
Severe COVID-19 disease, *n* (%)	26 (1.0)	25 (0.2)
Length of First COVID-19 Hospitalization, Days		
Mean (standard deviation)	10.69 (12.35)	11.48 (16.54)
Median (interquartile range)	6.5 (5, 11)	5.0 (4, 10)
Minimum, Maximum	1, 59	2, 76
Intensive care unit admission, *n* (%)	6 (0.23)	3 (0.03)
Invasive mechanical ventilation, *n* (%)	5 (0.19)	5 (0.05)
31-day post-COVID-19 hospitalization mortality, *n* (%)	0 (0.0)	0 (0.0)

Abbreviations: COVID-19, coronavirus disease 2019.

use of a large integrated healthcare system with a diverse and stable population. The KPSC's robust EHR database enabled assembly of this large cohort of individuals with DS that includes comprehensive, accurate capture of COVID-19 diagnosis, COVID-19 hospitalizations, and death, as well as extensive demographic and clinical covariates. We also used objective indicators of severe COVID-19 outcomes including mortality and use of invasive ventilation (determined based on measures of oxygenation of blood). Finally, we believe that the matched cohort design minimized selection bias.

Nonetheless, our study has limitations. Due to the observational nature of the retrospective, observational study design, results may be susceptible to residual confounding from factors that are related to DS and also affect the risk of COVID-19 infection and severe outcomes. For example, individual behaviors potentially impacting care-seeking behavior, respiratory hygiene, and the risk of COVID-19 are difficult to measure and control for between individuals with and without DS. However, we believe such confounding is minimized by the matched cohort design and multivariable analyses. Misclassification of SARS-CoV-2 infection may have occurred due to false-positive test results or erroneous diagnosis code recorded from claims; we believe that this misclassification is nondifferential between individuals with and without DS. Misclassification of DS diagnosis is theoretically possible in case of erroneous or missed diagnosis codes but is likely minimal given the comprehensiveness and accuracy of our EHR data. Finally, after the study period, several variants of SARS-CoV-2 have emerged in Southern California, including those seen in the United Kingdom (20I/501Y.V1/B.1.1.7) and South Africa (20H/501Y.V2/B.1.351) with increased infectivity and virulence [29]. The extent to which our study results can apply to later variants is less clear.

CONCLUSIONS

The CDC lists DS among the conditions that are at a higher risk of developing severe illness from COVID-19 [22]. Our findings confirm the risk and highlight that particular attention is warranted for the prevention, monitoring, and prompt treatment of COVID-19 in individuals with DS as well as promotion of COVID-19 vaccines.

Notes

Potential conflicts of interest. J. H. K. has received funding from Moderna and GlaxoSmithKline unrelated to this manuscript. M. J. L. has received funding for Advisory Board activities related to coronavirus disease 2019 from AstraZeneca and Moderna, and he received funding related to clinical trials from Moderna, Novavax, and Johnson & Johnson unrelated to this manuscript. Y. L. has received funding from GlaxoSmithKline, Seqirus, Moderna, and Pfizer unrelated to this manuscript. A. F. has received funding from Moderna, GlaxoSmithKline, Gilead, and Pfizer unrelated to this manuscript. H.-F. T. has received funding from Moderna and GlaxoSmithKline, unrelated to this manuscript, and serves on advisory boards for Janssen and Pfizer. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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