OBSERVATION: BRIEF RESEARCH REPORT

COVID-19 Mortality Risk in Down Syndrome: Results From a Cohort Study Of 8 Million Adults

Background: At the start of the coronavirus disease 2019 (COVID-19) pandemic, many national health organizations emphasized nonpharmacologic interventions, such as quarantining or physical distancing. In the United Kingdom, strict self-isolation ("shielding") was advised for those deemed to be clinically extremely vulnerable on the basis of the presence of selected medical conditions or at the discretion of their general practitioners.

Down syndrome features on neither the U.K. shielding list nor the U.S. Centers for Disease Control and Prevention list of groups at "increased risk." However, it is associated with immune dysfunction, congenital heart disease, and pulmonary pathology and, given its prevalence, may be a relevant albeit unconfirmed risk factor for severe COVID-19 (1).

Objective: To evaluate Down syndrome as a risk factor for death from COVID-19 through a comprehensive analysis of individual-level data in a cohort study of 8.26 million adults (aged >19 years), as part of a wider COVID-19 risk prediction project commissioned by the U.K. government (2).

Methods and Findings: We used QResearch, a population-level primary care database that has collected data for more

Table. Selected Clinical and Demographic Features of the Study Cohort, by Down Syndrome Status*

Variable	Persons Without Down Syndrome (*n* = 8 252 105)	Persons With Down Syndrome (*n* = 4053)
Male sex	4 109 205 (49.80)	1992 (49.15)
Age category		
19–29 y	1 562 167 (18.93)	1078 (26.60)
30–39 y	1 607 609 (19.48)	886 (21.86)
40–49 y	1 379 523 (16.72)	815 (20.11)
50–59 y	1 371 518 (16.62)	901 (22.23)
60–69 y	1 027 518 (12.45)	305 (7.53)
≥70 y	1 303 770 (15.8)	68 (1.67)
Median age at baseline (IQR), *y*	46 (25–62)	40 (29–52)
COVID-19 testing		
Test performed	351 524 (4.26)	300 (7.40)
Negative result	315 408 (3.82)	263 (6.49)
Positive result	36 391 (0.44)	37 (0.91)
Death from any cause during study	41 685 (0.51)	68 (1.68)
Death from COVID-19 during study	8457 (0.10)	27 (0.67)
Median age at death from COVID-19 (IQR), *y*	83 (75–89)	61 (52–64)
Death from causes other than COVID-19		
Pneumonia-related (ICD-10 codes: J18, J22, and J69)	5999 (0.09)	17 (0.49)
Other causes	27 229 (0.33)	24 (0.59)
COVID-19 hospital admission during study	19 057 (0.23)	41 (1.01)
BMI		
Mean (SD), kg/m^2	26.75 (5.61)	29.78 (6.67)
<18.5 kg/m^2	220 890 (2.68)	65 (1.60)
18.5–24.99 kg/m^2	2 744 076 (33.25)	919 (22.67)
25–29.99 kg/m^2	2 319 326 (28.11)	1110 (27.39)
30–34.99 kg/m^2	1 078 803 (13.07)	884 (21.81)
≥35 kg/m^2	612 835 (7.43)	833 (20.55)
Not recorded	1 276 175 (15.46)	242 (5.97)
In residential or nursing home	49 205 (0.60)	665 (16.41)
Ethnicity		
White	5 341 455 (64.73)	2933 (72.37)
Indian British	226 666 (2.75)	74 (1.83)
Pakistani British	147 518 (1.79)	75 (1.85)
Bangladeshi British	110 861 (1.34)	54 (1.33)
Other Asian British	144 947 (1.76)	44 (1.09)
Caribbean British	93 250 (1.13)	51 (1.26)
Black	197 899 (2.40)	56 (1.38)
Chinese British	82 385 (1.00)	11 (0.27)
Other ethnic group	305 290 (3.70)	113 (2.79)
Not recorded	1 601 834 (19.41)	642 (15.84)
Smoking status		
Nonsmoker	4 721 643 (57.22)	3746 (92.43)
Former smoker	1 752 836 (21.24)	116 (2.86)
Light (1–9 cigarettes/d)	1 094 462 (13.26)	59 (1.46)
Moderate or heavy (≥10 cigarettes/d)	307 513 (3.73)	11 (0.27)
Not recorded	375 651 (4.55)	121 (2.99)

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Table–Continued

Variable	Persons Without Down Syndrome (*n* = 8 252 105)	Persons With Down Syndrome (*n* = 4053)
Alcohol status		
Nondrinker	4 230 856 (51.27)	3091 (76.26)
Trivial (<1 unit/d)	1 217 490 (14.75)	398 (9.82)
Light (1–2 units/d)	601 619 (7.29)	96 (2.37)
Moderate or heavy (≥3 units/d)	534 676 (6.48)	38 (0.94)
Not recorded	1 667 464 (20.21)	430 (10.61)
Medical history/comorbid conditions		
COPD	193 124 (2.34)	9 (0.22)
Asthma	1 124 504 (13.63)	550 (13.57)
Rare lung diseases†	45 149 (0.55)	32 (0.79)
Pulmonary hypertension or pulmonary fibrosis	6751 (0.08)	80 (1.97)
Coronary disease	292 089 (3.54)	15 (0.37)
Previous stroke	177 150 (2.15)	62 (1.53)
Atrial fibrillation	200 282 (2.43)	10 (0.25)
Heart failure	96 171 (1.17)	54 (1.33)
Venous thromboembolism	143 987 (1.74)	111 (2.74)
Peripheral vascular disease	60 923 (0.74)	16 (0.39)
Type 1 diabetes	38 849 (0.47)	75 (1.85)
Type 2 diabetes	531 493 (6.44)	161 (3.97)
Congenital heart disease	42 128 (0.51)	792 (19.54)
Dementia	80 519 (0.98)	338 (8.34)
Epilepsy	108 695 (1.32)	400 (9.87)
Cerebral palsy	8896 (0.11)	18 (0.44)
Severe mental illness	918 809 (11.13)	353 (8.71)
Blood cancer	34 008 (0.41)	29 (0.72)
Leukotriene antagonist/LABA therapy	36 552 (0.44)	24 (0.59)
Prescribed regular steroids	92 505 (1.12)	29 (0.72)
Osteoporotic fracture	325 773 (3.95)	98 (2.42)
Rheumatoid arthritis or SLE	82 212 (1.00)	26 (0.64)
Chronic liver disease	90 868 (1.10)	47 (1.16)
On shielded patient list‡	330 833 (4.01)	327 (8.07)

BMI = body mass index; COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019; ICD-10 = International Classification of Diseases, 10th Revision; IQR = interquartile range; LABA = long-acting β_2-agonist; SLE = systemic lupus erythematosus.
* Values are numbers (percentages) unless otherwise indicated. Rows with <5 persons have been removed.
† Encompasses various pathologies, such as cystic fibrosis and extrinsic allergic alveolitis.
‡ Persons on the shielded list were advised to follow strict self-isolation measures to reduce exposure to COVID-19 and were eligible for a support package that included food parcel and medicine deliveries. For the Down syndrome group, 8.07% were on the nationally maintained list of patients who were advised to shield, which will be because of a combination of small proportions of persons with Down syndrome having recorded diagnoses of conditions conferring "clinical vulnerability" and nonrecognition of Down syndrome as a risk factor for adverse outcomes.

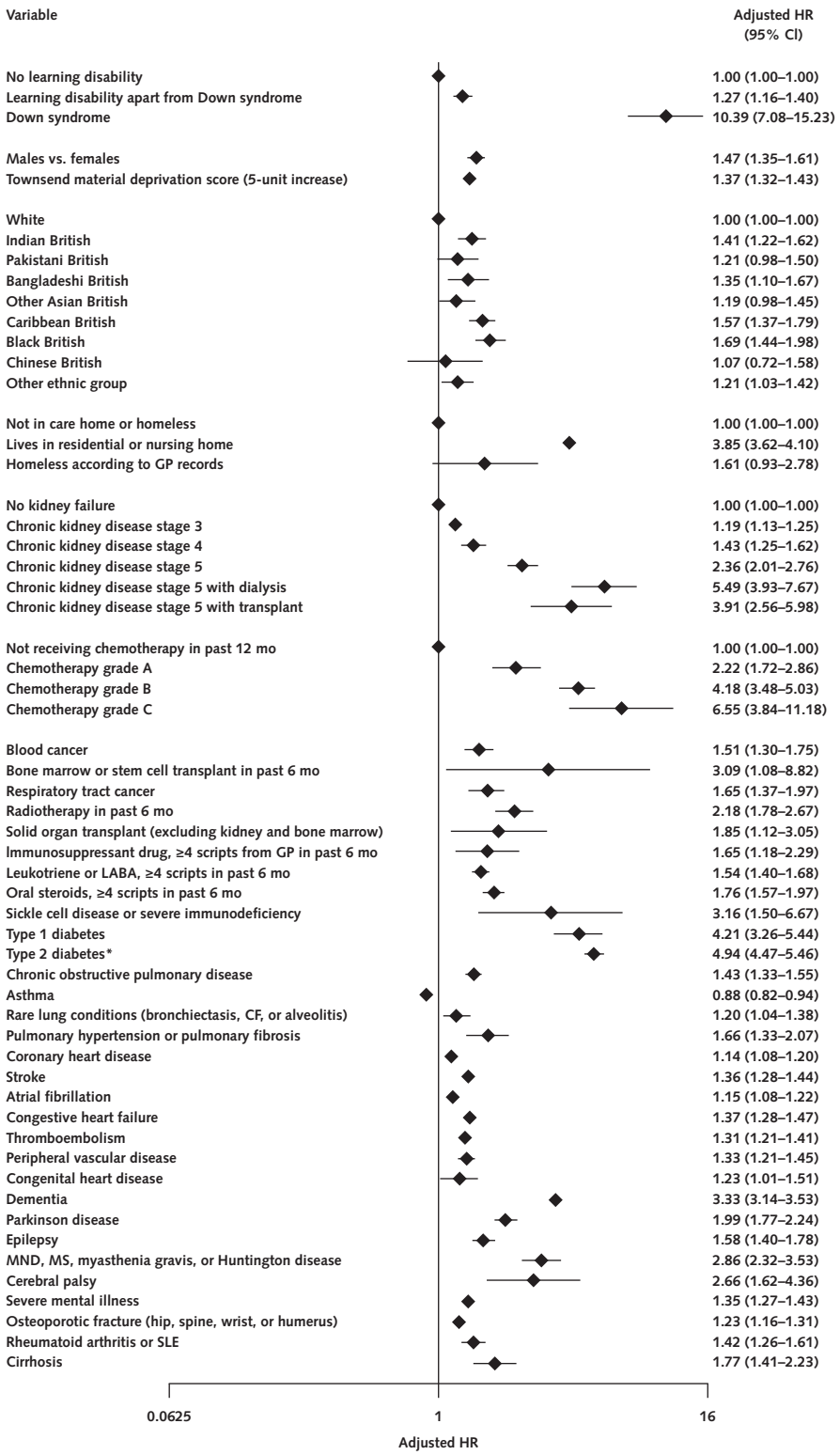
than 35 million persons in England since 1998 and is linked at the individual patient level to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) testing results from Public Health England, hospital episode statistics, and the Office of National Statistics death registry. Data extracted included age, sex, ethnicity, alcohol intake, smoking status, body mass index (BMI), a range of preexisting comorbid conditions, and concurrent medications. The primary outcome of interest was COVID-19 mortality in or out of the hospital, defined as confirmed or suspected COVID-19 on the death certificate or death within 28 days of a confirmed SARS-CoV-2 infection in the study period. The secondary outcome of interest was hospital admission related to COVID-19. The study period was 24 January 2020 (first confirmed SARS-CoV-2 infection in the United Kingdom) to 30 June 2020. We used Cox proportional hazards models to estimate adjusted hazard ratios (HRs) with 95% CIs, accounting for death from non–COVID-19 causes as a competing event by censoring all persons who did not have the outcome of interest at the study end date. We tested for interactions between Down syndrome and age, BMI, and sex.

The **Table** shows selected demographic and clinical characteristics for the cohort. Of 8.26 million adults in the study cohort, 4053 had Down syndrome. Sixty-eight persons with Down syndrome died, 27 (39.7%) of COVID-19, 17 (25.0%) of pneumonia or pneumonitis, and 24 (35.3%) of other causes. Of the 8 252 105 persons without Down syndrome, 41 685 died, 8457 (20.3%) of COVID-19, 5999 (14.4%) of pneumonia or pneumonitis, and 27 229 (65.3%) of other causes.

Adjusted for age and sex, the HR for COVID-19–related death in adults with versus without Down syndrome was 24.94 (95% CI, 17.08 to 36.44). After adjustment for age, sex, ethnicity, BMI, dementia diagnosis, care home residency, congenital heart disease, and a range of other comorbid conditions and treatments (**Table**), the HR for COVID-19–related death was 10.39 (CI, 7.08 to 15.23); for hospitalization, it was 4.94 (CI, 3.63 to 6.73) (**Figure**). There was no evidence of interactions between Down syndrome and age, sex, or BMI. The HR for death was not affected by further adjustment for smoking status and alcohol intake (HR, 10.12 [CI, 6.90 to 14.84]). For those with learning disabilities other than Down syndrome, the adjusted HR for COVID-19–related death was 1.27 (CI, 1.16 to 1.40).

Discussion: We estimated a 4-fold increased risk for COVID-19–related hospitalization and a 10-fold increased risk for COVID-19–related death in persons with Down syndrome, a group that is currently not strategically protected. This was

Figure. Adjusted HR (95% CI) for the association between Down syndrome and death from COVID-19.



Adjusted for the variables shown, deprivation, fractional polynomial terms for body mass index (BMI), and age. The model includes fractional polynomial terms for age, BMI, and interaction terms between age terms and type 2 diabetes. We used the QResearch database, version 44. The study period was 24 January 2020 to 30 June 2020. CF = cystic fibrosis; COVID-19 = coronavirus disease 2019; GP = general practitioner; HR = hazard ratio; LABA = long-acting β_2-agonist; MND = motor neurone disease; MS = multiple sclerosis; SLE = systemic lupus erythematosus.
* HR for type 2 diabetes reported at mean age.

after adjustment for cardiovascular and pulmonary diseases and care home residence, which our results suggest explained some but not all of the increased risk. These estimated adjusted associations do not have a direct causal interpretation because some adjusted variables may lie on causal pathways, but they can inform policy and motivate further investigation. Participation in day care programs or immunologic deficits could be implicated, for example. Down syndrome is the most common genetic cause of intellectual disability, with multiorgan manifestations (3). Predisposition to pneumonias and acute respiratory distress syndrome in children, airway anomalies, pulmonary hypoplasia, and inhibited pulmonary angiogenesis have been reported (4, 5).

We are unaware of the effects of Down syndrome on COVID-19 outcomes being reported elsewhere yet during this pandemic. Novel evidence that specific conditions may confer elevated risk should be used by public health organizations, policymakers, and health care workers to strategically protect vulnerable individuals.

Ashley Kieran Clift, MA, MBBS
University of Oxford
Oxford, United Kingdom

Carol A.C. Coupland, PhD
University of Nottingham
Nottingham, United Kingdom

Ruth H. Keogh, DPhil
London School of Hygiene & Tropical Medicine
London, United Kingdom

Harry Hemingway, PhD
University College London, Health Data Research UK, and National Institute for Health Research Biomedical Research Centre
London, United Kingdom

Julia Hippisley-Cox, MD
University of Oxford
Oxford, United Kingdom

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Corresponding Author: Julia Hippisley-Cox, MD, Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, Woodstock Road, Oxford OX2 4GG, United Kingdom; e-mail, julia.hippisley-cox@phc.ox.ac.uk.

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