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COVID-19-EPIDEMIC :

COVID-19 and risk factors for hospital admission, severe disease and death – a rapid review, 4th update

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Key messages

This rapid review is the 4th update in the series "*COVID-19 and risk factors for hospital admission, severe disease and death*" replacing our previous report published on November 15th, 2020. In this review, only peer-reviewed population-based studies with more than 5000 laboratory test positive COVID-19 cases are included.

The findings are based on searches in MEDLINE and Embase on March 31st, 2021, updated by a neural network search in Microsoft Academic Graph on April 14th, 2021. One researcher screened the search results, and two researchers selected studies for inclusion and synthesised the results. Experts in the field assisted with study inclusion and provided helpful input during the review process. In the current situation, there remains an urgent need for identifying the most important evidence timely. Hence, we opted for this rapid approach despite an inherent risk of overlooking evidence or making misguided judgements.

We included ten studies that reported results from multivariate analyses of demographic and medical risk factors. We excluded risk factors that constituted laboratory findings, clinical signs and symptoms of COVID-19. Three studies were from UK, and one from Denmark, Norway, Mexico, South Korea, Spain, Sweden, and from USA. Four out of ten studies only reported data on the adult population.

Meta-analysis was not feasible, and the main results of this rapid review are therefore presented in tabular form and narratively. Risk factors associated with (i) hospitalisation, (ii) severe/critical disease, and (iii) COVID-19-related death are reported separately. The included studies provide a granular overview of risk factors based on population-based studies. Although our findings are representative for large parts of the population, some groups are less well represented, especially people with rare conditions. For example, in this update, more studies included populations under 18 years, but the results may still not be representative for this population group as the total number of registered incidents remain small. Other population and patient groups, which are not captured by the included studies, will require further research.

Risk factors for hospitalisation related to COVID-19

Six studies assessed risk factors for hospitalisation related to COVID-19. Overall, age, comorbidities and severity of comorbidities were found to be strong predictors of hospital admission. Five out of six studies provided a granular overview of adjusted hazard ratios (HRs)/odds ratios (ORs) for a broad selection of comorbidities, conditions and ongoing treatments. Four studies showed a clear dose response relationship between increasing age and risk of hospital admission. Four studies reported an increased adjusted HR/OR/ relative risk (RR) for hospital admission in men and for people overweight and obese. Based on three studies,

most non-whites or foreign born were at increased risk of admission. Two studies reported increasing risk of admission by number of co-existing comorbidities. Severe kidney disease, diabetes, ongoing chemotherapy, severe immunodeficiency, heart failure, and Down syndrome stand out with a greater associated risk of hospital admission (OR/HR >=3).

Risk factors for developing more severe or critical COVID-19 (ICU treatment)

Four studies assessed risk factors for ICU admissions related to COVID-19. Two studies provided a detailed overview of comorbidities and demographic factors, and two studies presented mainly demographic factors. Overall, age was found to be the strongest predictor of severe COVID-19, with increasing risk until the late 60-70s, and then falling again. This admission pattern may reflect differing treatment approaches than severity of disease. Furthermore, male sex, diabetes, asthma, chronic kidney disease, tuberculosis and Down syndrome were associated with increased risk for ICU admission related to severe COVID-19.

Risk factors for COVID-19-related death

Nine studies assessed risk factors for COVID-19-related death. All studies provided a granular overview of risk factors. Overall, increasing age was found to be the strongest predictor of COVID-19-related death, while increased risk was also observed for male sex, number of and severity of most comorbidities. Ethnicity other than white was consistently associated with modest but increased risk of death, with Blacks having the highest risk of death. Two studies found increasing risk of death with increasing degree of deprivation. Kidney disease, diabetes mellitus type I and II, dementia, ongoing chemotherapy, organ transplantation, severe immunodeficiency, major psychiatric disorders treated with antipsychotics, cerebral palsy and Down syndrome were reported as the strongest predictors of COVID-19 related death (OR/HR >=3). Most singular comorbidities were associated with an increased risk of death, but mixed results were observed for obesity.

Conclusion

Through this 4th revision, previous findings are strengthened and expanded. The elderly are clearly the main group at risk of hospital admission, severe disease, and death if infected by COVID-19. Most comorbidities appear to increase risk, with increasing number of and severity of comorbidities contributing to a further increase in the overall risk. Male sex, non-white ethnicity and deprivation are also associated with increased risk.

Hovedbudskap

Denne hurtigoppsummeringen er den fjerde oppdateringen av «*Covid-19 og risikofaktorer for sykehusinnleggelse, alvorlig sykdom og død*», som erstatter den forrige versjonen publisert 15. november, 2020. I denne oppdaterte versjonen inkluderte vi kun fagfellevurderte populasjonsbaserte studier med over 5000 deltagere med laboratoriebekreftet covid-19.

Resultatene som presenteres i denne oppsummeringen er basert på litteratursøk i MEDLINE og Embase den 31. mars 2021, og et «neural network» søk i Microsoft Academic Graph den 14. april 2021. Én forsker gjennomgikk søkeresultatene, og to forskere valgte ut studier for inklusjon, uthenting av data og sammenstilling av resultater. Eksperter i relevante fagfelt bidro i vurderingen av studier for inklusjon samt bisto med faglig input fortløpende.

Sett i lys av dagens situasjon er det et stort behov for å raskt kunne innhente evidensbasert kunnskap om populasjonsgrupper som er sårbare for alvorlige utfall knyttet til covid-19. Derfor valgte vi en hurtigoppsummeringstilnærming for denne rapporten på tross av den potensielle risikoen for å overse viktig informasjon eller å foreta forhastede vurderinger.

Vi inkluderte ti studier som rapporterte resultater fra multivariate analyser av demografiske og medisinske risikofaktorer. Vi ekskluderte risikofaktorer rapportert som biologiske markører, kliniske funn og symptomer på covid-19. De inkluderte studiene var fra disse landene; tre fra Storbritannia, og én fra hvert av følgende land: Danmark, USA, Mexico, Norge, Spania, Sverige og Sør-Korea. Fire av ti studier rapporterte kun data om den voksne befolkningen.

Sammenstilling av resultatene i metaanalyser ble ikke vurdert som hensiktsmessig, så hovedresultatene i denne hurtigoppsummeringen blir presentert narrativt og i tabellformat. Risikofaktorer assosiert med (i) sykehusinnleggelse, (ii) alvorlig sykdomsforløp og (iii) død knyttet til covid-19 rapporteres separat nedenfor. Selv om funnene fra denne rapporten kan ansees som representative for store deler av befolkningen, er visse grupper underrepresentert i studiene, spesielt personer med sjeldne tilstander. I denne oppdateringen identifiserte vi flere studier som inkluderte populasjoner under 18 år, men det er fortsatt usikkert om funnene kan generaliseres til denne aldersgruppen da antall deltagere med relevante utfall fortsatt er lavt. Andre befolknings- og pasientgrupper, som muligens ikke er fanget opp av de inkluderte studiene, vil også kreve videre forskning.

Risikofaktorer for sykehusinnleggelse relatert til covid-19

Seks studier undersøkte risikofaktorer for sykehusinnleggelse relatert til covid-19. Samlet sett var høy alder, komorbiditet og alvorlighetsgrad av komorbide lidelser assosiert med økt risiko for sykehusinnleggelse. Den komorbide tilstandens alvorlighetsgrad og antall komorbide lidelser påvirket risikoen i stor grad. Alle studiene rapporterte resultater fra multivariate analyser med HRs eller ORs som effektestimater for et stort antall demografiske og medisinske risikofaktorer. Fire studier viste en klar dose-respons sammenheng mellom økende alder og økt risiko for sykehusinnleggelse. Videre rapporterte fire studier om økt risiko for sykehusinnleggelse for

menn og for personer med overvekt og fedme. Tre studier rapporterte også økt risiko for sykehusinnleggelse blant personer med ikke-hvit etnisitet. Videre ble alvorlig nyresykdom, diabetes, pågående cellegiftkur, hjertesvikt, alvorlig immunsvikt og Downs syndrom assosiert med en betydelig forhøyet risiko for sykehusinnleggelse (OR/HR >=3).

Risikofaktorer for alvorlig eller kritisk covid-19 forløp og innleggelse ved intensivavdeling

Fire studier undersøkte risikofaktorer for innleggelse ved intensivavdeling eller alvorlig sykdomsforløp på grunn av covid-19. To studier presenterte en detaljert oversikt over sykdomstilstander og demografiske risikofaktorer, og to studier presenterte hovedsakelig demografiske risikofaktorer. Overordnet var det høyest risiko for alvorlig sykdomsforløp og intensivinnleggelser alder, med økende risiko frem til 60-70 år, deretter avtar risikoen noe. Denne trenden reflekterer antakelig ulike behandlingstilnærminger for ulike aldersgrupper. Videre var mannlig kjønn, diabetes, astma, kronisk nyresykdom, tuberkulose og Down syndrom assosiert med en forhøyet risiko for alvorlig sykdomsforløp.

Risikofaktorer for covid-19 relatert død

Ni studier undersøkte risikofaktorer for covid-19 relatert død. Samlet var økende alder den sterkeste prediktoren for covid-19 relatert død. Videre ble ikke-hvit etnisitet, mannlig kjønn, antall og alvorlighetsgrad av komorbide lidelser identifisert som risikofaktorer for covid-19 relatert død. To studier fant også en økt risiko for covid-19 relatert død ved økt grad av fattigdom. Alvorlig nyresykdom, diabetes, demens, pågående cellegiftkur, gjennomgått organtransplantasjon, alvorlig immunsvikt, psykiske lidelser behandlet med antipsykotika, cerebral parese og Downs syndrom ble rapportert som de sterkeste medisinske prediktorene for covid-19 relatert død (OR/HR >=3). Forhøyet risiko for død ble funnet for de fleste kroniske lidelsene, med blandede resultater for fedme.

Konklusjon

Funnene i denne 4. oppdateringen er i tråd med resultatene som er rapportert i de tidligere versjonene. Det er tydelig at eldre mennesker er den populasjonen med høyest risiko for sykehusinnleggelse, alvorlig sykdomsforløp og død relatert til covid-19. De fleste kroniske lidelsene er assosiert med forhøyet risiko, hvor både antall komorbiditeter og komorbiditetenes alvorlighetsgrad har stor betydning for den overordnede risikoen for de ulike covid-19 utfallene inkludert i denne hurtigoppsummeringen. Økt risiko ble også observer blant for menn, personer med ikke-hvit etnisitet og de som lever i fattigdom.

Table of content

Problem statement

In relation to the ongoing COVID-19 outbreak, it is important to gather information about which patient groups are most at risk of severe outcomes. The outbreak team at the Norwegian Institute of Public Health has asked us to update a rapid review of the existing research on risk factors for hospitalisation, serious/critical COVID-19, or death, published November 15th 2020 (1).

Methods

Literature search

To investigate which demographic and medical risk factors are associated with hospitalisation, severe/critical disease, and COVID-19-related death, we searched for studies with more than 5000 participants that had laboratory confirmed COVID-19 and reported risk factors for the three main outcomes. The search strategy from our previous report, was re-run on March 31st, 2021 in the MEDLINE and Embase databases for studies published in the period 01.10.2020 - 31.03.2021. After title and abstract screening on April 14th, 2021 a neural network search was conducted on identified articles to capture further relevant articles using EPPI reviewer's neural network search function using Microsoft Academic Graph's database (2).

Inclusion criteria:

Population:	More than 5000 confirmed COVID-19 cases from the general population. COVID-19 cases should be defined by PCR/ antigen testing.
Outcome:	Hospital admission, ICU admission, ICU with ventilation, severe disease, death
Study types:	Cohort studies, prospective studies, retrospective studies

Study selection

We included publications assessing the importance of various demographic and medical risk factors for the risk of COVID-19-related hospitalisation, severe/critical disease and death. The factors examined were age, sex, ethnicity, deprivation, body mass index (BMI), medical conditions, underlying comorbidities, as well as substance use. Clinical symptoms and laboratory-based risk factors were not included in this report. In this fourth update we excluded studies with less than 5000 participants due to power considerations. Only studies where the relative importance of various risk factors were assessed using multivariate statistical models were included. We excluded systematic reviews and studies only assessing risk factors from unadjusted univariate or bivariate analyses.

Review process

One researcher (JH) performed title and abstract screening. Two researchers (TB, JH) reviewed the studies in full text, selected studies for inclusion, and extracted and summarised data/results from included studies in tables. A group of experts in the field assisted during the study inclusion process. Two researchers (TB, JH) independently performed a formal quality assessment with the Newcastle-Ottawa quality assessment scale of included papers (3), but this rapid review does not include a grading of the certainty of evidence. Therefore, the results should be interpreted with caution.

Peer review

Siri Feruglio (senior medical officers, Norwegian Institute of Public Health), Helena Niemi Eide and Jacob Berild (medical officer, Norwegian Institute of Public Health) critically reviewed the draft before publication. We thank our colleagues for their excellent comments and feedback.

Results

Description of studies

Results of the literature search

We identified 4,823 references through the systematic literature searches in MEDLINE and Embase. JH screened all probable titles and abstracts in EPPI reviewer (4). We identified a total of 23 studies for full text screening, 9 studies remained after full text screening. To identify further relevant studies, we performed a neural network search in Microsoft Academic Graph (2) on the identified articles after title and abstract screening. Via the neural network search, we identified an additional 4 studies for full text screening. In total, we read 27 references in full text, of which 10 articles matched our inclusion criteria. Of these, 5 studies were also included in the previous report. Figure 1 shows a graphical representation of our search and screening methodology.

Study selection

Following full text screening, studies were discussed with a group of experts determining final inclusion. We included 10 studies that reported results from multivariate analyses of demographic (e.g. sex, ethnicity, smoking) and medical risk factors (5-14). Three studies were from the UK (5, 6, 9) , and one from Denmark (8), Norway (13), Mexico (12), South Korea(11), Spain (14), Sweden (10), and USA (7). Studies with granular demographic and comorbidity data were summarised in tabular form, less granular studies are descriptively summarised in the text. Four out of ten studies reported only data on the adult population. All studies were published in international peer reviewed journals.

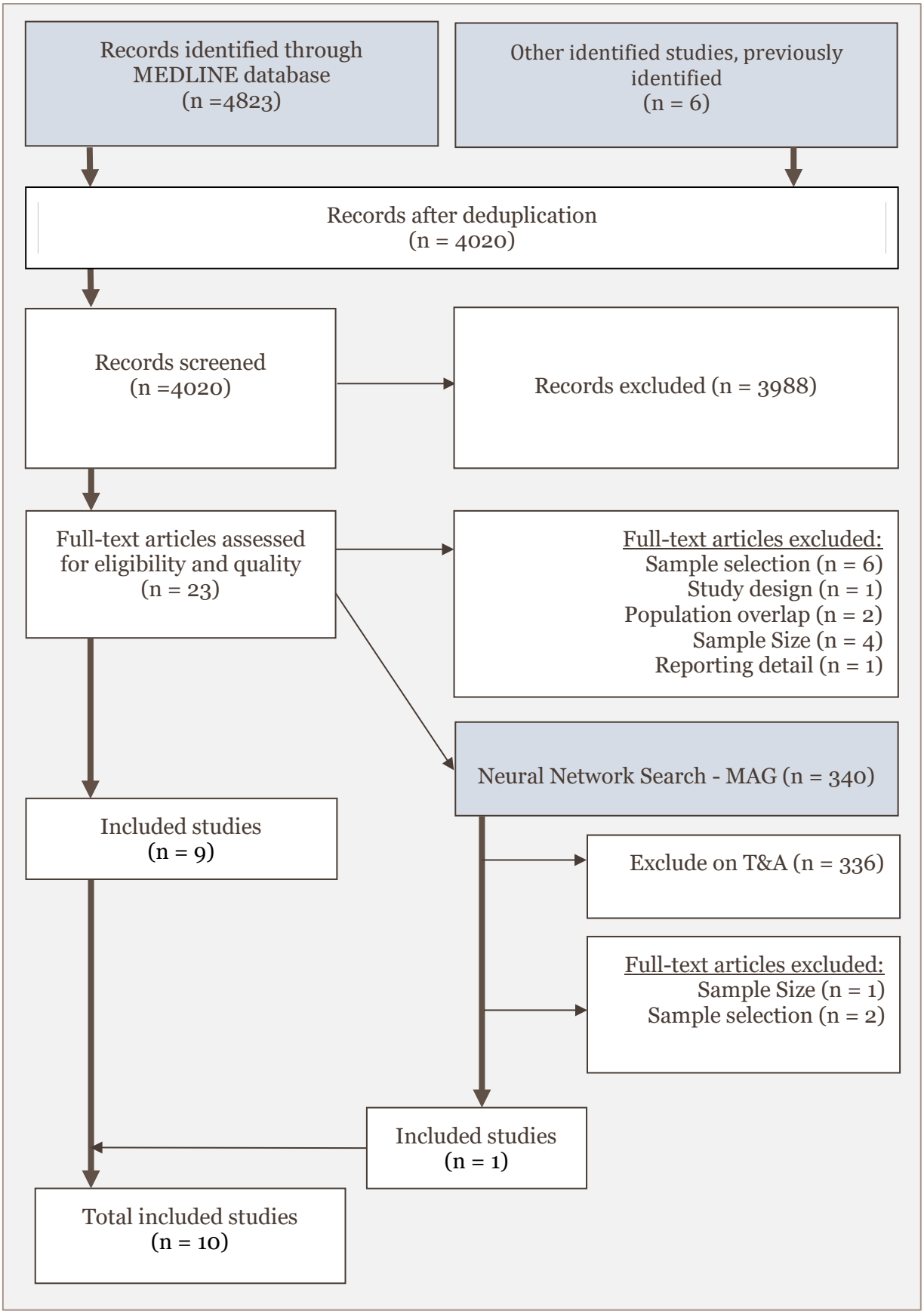

Figure 1. Flow diagram of search strategy and study inclusion

Included studies

We included 10 studies (Table 1.) and excluded 17 studies (Appendix 2).

Table 1. Included reviews

First author	Study type, timeframe	Study population	Outcomes reported	Sample size					Covariates included in multivariate model
				Total	COVID - 19 positive*	Hospitalised	Severe disease	Died	
Barron (5) England	Retrospective study, Feb – May 2020	Individuals registered with a general practice (age group: 0-80+ (lowest age group 0-39)	Death (Death in hospital with COVID-19 in the overall population)	61,414,470	Unclear			23,698	Model 1: Age, sex, ethnicity, deprivation, geographic region, coronary heart disease, cerebrovascular disease and heart failure. Model 2: Age, sex, ethnicity, deprivation, geographic region, and diabetes status
Bergman (10) Sweden	Matched cohort study, Jan – Sep 2020	all cases confirmed in Sweden (excluding: care home residents, admitted prior to study start)	non-ICU and ICU hospitalization, all-cause mortality	518,739	87,069	13,589	2494		Age, sex, Place of birth, education, income, home services, comorbidities, medications
Burn (14) Spain	Cohort registry study, Mar – May 2020	All individuals in primary care registry in Catalonia	Diagnosis, hospitalisation, Death	5,586,521	102,002	16,901		5273	Age and sex, comorbidities
Clift (6) England	Population based cohort study, Jan -Apr 2020	Adults in general practice (age group 19-100)	1.Hospitalisation 2. Death (Death from COVID-19 either in hospital or outside hospital)	6,083,102	Unclear	10,776		4,384	Age, BMI, deprivation score, residency, ethnicity, kidney disease, cancer, diabetes, lung disease, heart disease, neurologic disease, mental illness, and more. All models were stratified by sex.
Hernandez-Vasquez (12) Mexico	Cross-sectional study Feb – May 2020	Covid -19 positive cases (0-85+))	Death	51,053				5,233	Age, gender, and smoking status, HBP, diabetes, obesity, asthma, immunosuppression, other CVDs, chronic obstructive pulmonary disease (COPD), and chronic kidney disease, multimorbidity
Lee (11) South Korea	Population based cohort study Jan – May 2020	Adults registered in nationwide health insurance database	Death	234,427	7,339		927	227	Included one medication at a time with all variables regarding comorbidities and significant variables in the univariable analyses and one comorbidity at a time with all variables regarding medications and significant variables in the univariable analyses.
Petrilli (7) USA	Prospective cohort study Mar -Apr 2020	Adults in an academic medical centre in New York/Long Island (age 19-75+)	Hospitalisation	11,544	5,279	2,741	990		Age at time of testing, sex, ethnicity, hypertension, hyperlipidemia, coronary artery disease, heart failure, pulmonary disease, malignancy, diabetes, obesity
Reilev (8) Denmark	Cohort study Feb – May 2020	Nationwide cohort tested for COVID-19 (age group 0-90+ (0-19 (2.7%))	Hospitalisation severe disease, death	410,697	11,122	2,254	314	577	Age, sex, chronic lung disease, hypertension, ischaemic heart disease, heart failure, atrial fibrillation, stroke, diabetes, dementia, cancer, chronic liver disease, kidney disease, alcohol abuse, substance abuse, major psychiatric disorders, organ transplantation, overweight/ obesity, and/or rheumatoid arthritis/connective-tissue disease. (information for ICU outcome)
Telle (13) Norway	Prospective cohort Feb – Jun 2020	All confirmed COVID-19 cases by end of June 2020	Hospitalisation, severe disease (mechanical ventilation), death	8,569	8,569	1,200	146	223	Age, sex, place of birth, comorbidity proxy, nursing home resident
Williamson (9) UK	Cohort registry study Feb -May 2020	Adult primary care patients (age group 18-80+)	Death	17,278,392				10,926	Age, sex, BMI, smoking, IMD, hypertension/high blood pressure, asthma, chronic heart disease, diabetes, non-hematological cancer, hematological malignancy, reduced kidney function, liver disease, stroke or dementia, other neurological disease, organ transplant, asplenia, rheumatoid arthritis, lupus or psoriasis, other immunosuppressive condition.

We distinguish between studies that explore risk factors associated with

(i) hospitalisation related to COVID-19 (N=6)(6-8, 10, 13, 14),

(ii) development of more severe /critical COVID-19 (N=4) (7, 8, 10, 13),

(iii) COVID-19-related death (N=7) (5-11, 13)

Quality assessment

We performed quality assessment of included studies with the Newcastle–Ottawa Scale (NOS) for cohort studies (6-9, 14) and case-control studies (5, 10) (Table 2.) The NOS assesses methodological quality relating to three aspects of a study (Selection, Comparability and Outcome) and categorises studies as being of good, fair or poor methodological quality, based on level of fulfilment for each of the three criteria (maximum score is 9 points). We set no cut-off for included studies by total quality score.

Table 2. Newcastle–Ottawa Scale quality assessment

First author	Selection				Comparability	Outcome/Exposure			Total score
	1	2	3	4	5	6	7	8	
Barron	1(a)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(a)	1(a)	9
Bergman	1(a)	1(a)	1(a)	1(a)	2(a,b)	1(a)	1(a)	1(a)-	9
Burn	1(a)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(b)	1(a)	9
Clift	1(b)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(a)	1(a)	9
Hernandez-Vasquez	1(b)	1(a)	1(a)	1(a)	1(a)	1(b)	1(a)	1(a)	8
Lee	1(b)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(a)	1(a)	9
Petrilli	1(b)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(a)	1(a)	9
Reilev	1(b)	1(a)	1(a)	1(a)	2(a,b)/0[i]	1(b)	1(a)	1(a)	9/7[i]
Telle	1(b)	1(a)	1(a)	1(a)	1(a)	1(b)	1(a)	1(a)	8
Williamson	1(b)	1(a)	1(a)	1(a)	2(a,b)	1(b)	1(a)	1(b)	9

[i] For ICU admission outcome, only descriptive information was provided in text

Risk factors for hospitalisation related to COVID-19

Brief summary: Six studies (6-8, 10, 13, 14) assessed risk factors for hospitalisation related to COVID-19. All studies provided a granular overview of predicting factors. Results are listed side by side in Table 3. Overall, age, comorbidities and severity of disease were found to be strong predictors of hospital admission. Heart failure, kidney disease, diabetes, Down syndrome and ongoing chemotherapy is reported to have an especially high risk. Some evidence suggests that male sex and ethnicity is associated with increased risk of hospital admission (6, 7, 10).

Bergman et al (10) conducted a nationwide, registry-based study to investigate potential risk factors for diagnosis, hospitalisation, and mortality. The study population comprised all COVID-19 cases confirmed in Sweden by mid-September 2020 and 434,081 randomly sampled general population controls. Older age was the strongest risk factor for hospitalisation, after controlling for other risk factors, the odds of hospitalisation increased until 59 years, then decreased slightly between 60-79 (although generally remaining high), to increase again from 80+. Persons below 20 years of age were the least likely to be admitted. Male sex and the presence of at least one investigated comorbidity or prescription medication were associated with hospitalisation. The comorbidities associated most strongly with hospitalisation were Down syndrome, diabetes, kidney disease and organ transplantation. Cardiovascular disease, COPD, asthma, and immunodeficiency were weakly associated with hospitalisation, after adjustment for other risk factors.

The authors point out that the presence of some medical conditions, especially mild conditions, may be underestimated because primary-care diagnoses and complete histories of medical conditions were not available.

Burn et al (14) used patient-level data from the Information System for Research in Primary Care (SIDIAP) to summarise COVID-19 outcomes in Catalonia, Spain. The authors included 5,586,521 individuals from the general population (40,999 care home residents were excluded), 102,002 of these had an outpatient diagnosis of COVID-19, 16,901 were hospitalised with COVID-19, and 5,273 died after either being diagnosed or hospitalised with COVID-19 between March 1st and May 6th 2020. Those with older age and males had an increased risk for hospitalisation. Among the comorbidities, type 2 diabetes, dementia, obesity, and kidney disease were most strongly associated with hospitalisation. Risk of hospitalisation increased with increasing Charlson Comorbidity Index.

The authors point out that the associations which they describe should be interpreted in the context of the first wave of COVID-19 in Catalonia. Although PCR-testing data were linked in the registry to patients, the authors also included patients with clinical diagnosis only as PCR were not routinely performed in the out-patient setting at the time. It is unclear how much capacity limitations during this period impacted hospital admissions.

Clift et al (6) reported characteristics of hospitalisation in a nationwide cohort comprising 1,205 general practices in England with linkage to COVID-19 test results, Hospital Episode Statistics,

and death registry data. The results in detail, based on 10,776 admitted COVID-19 cases in the study period January 24th to April 30th, 2020 are presented in Table 3 stratified by sex. Hospital admission was defined as an ICD-10 code for either confirmed or suspected COVID-19, or new hospital admission associated with a confirmed SARS-CoV-2 infection in the study period. The authors report increased risk for all ethnicities compared to non-Hispanic whites, and most of the assessed comorbidities. Interestingly, the adjusted hazard ratios for body mass index, age, and the interaction between age and type 2 diabetes for hospital admissions due to COVID-19 showed higher risks associated with younger ages (Figure A, B in supplementary table of original study). The authors found the highest risk of hospitalisation for populations undergoing chemotherapy, followed by individuals suffering from severe kidney disease.

The authors point out that no systematic community testing was performed and that only those unwell enough to attend hospital were tested. This, they conclude would overestimate risks of severe outcomes in those who tested positive.

Petrilli et al (7) investigated risk factors associated with admission to hospital based on a prospective cohort study with 5,279 laboratory confirmed COVID-19 cases in New York City, USA, between March 1st, 2020 and April 8th, 2020, with complete follow-up through May 5th. 2,741 participants were admitted to hospital, of whom 1,904 were discharged alive without hospice care and 665 were discharged to hospice care or died. The strongest risk factor for hospital admission was age, with an OR of >2 for all age groups older than 44 years and OR 37.9 (95% confidence interval (CI) 26.1 to 56.0) for ages 75 years and older. Other risk factors were heart failure (OR 4.4, 2.6 to 8.0), male sex (OR 2.8, 2.4 to 3.2), chronic kidney disease (OR 2.6, 1.9 to 3.6), and BMI above normal weight range (e.g., for BMI >40: OR 2.5, 1.8 to 3.4). The authors also found a reduced OR for current and former smokers but increased OR for those with unknown smoking status (15% of participants).

The authors point out that data on patients not admitted to hospital were more limited and might not have had reported a less detailed medical history. In addition, this limitation may have been further exacerbated by that patients treated and discharged from the emergency department were not commonly tested and thus omitted from analysis unless later admitted to the hospital. As this was a single centre study, some not admitted patients might have been admitted to other institutions, and some discharged patients might have been readmitted elsewhere with critical illness or could have died post-discharge.

Reilev et al (8) reports characteristics of hospital admissions in a nationwide cohort comprising 11,122 confirmed COVID-19 cases in Denmark starting February 7th, 2020 until May 19th, 2020. In general, the authors observed only minor differences in age, sex, medical history and prior drug use between PCR positive cases and test-negative individuals. Among all PCR-positive cases, the median age was 48 years. Eighty percent of the PCR positive cases were community-managed and 20% were hospitalised, with more than 60% among cases hospitalised being older than 70 years. Twenty-two percent of those who died were managed in the community. Fifteen percent of community-managed cases had two or more comorbidities, whereas the corresponding proportion was 56% for hospitalised cases. The majority of hospitalised cases were admitted on the date of the positive PCR test (57%). The strongest predictors for hospital admission were age and number of comorbidities. Most major chronic diseases were associated with hospitalisation, with ORs ranging from 1.3–1.4 (e.g. stroke, ischaemic heart disease) to 2.6–

3.4 (e.g. heart failure, hospital-diagnosed kidney disease, organ transplantation). Detailed findings are listed in table 3, side by side with other relevant studies.

The authors point out that test strategy in Denmark was initially directed at those who were most sick and potentially in need of medical care. This test strategy may have contributed to an overestimation of the case fatality and the proportion of hospitalised cases. They also report a strict, early lockdown with hospital capacity never being overwhelmed. The communicated seriousness and ease of healthcare access might also have influenced patients to present early, and a low threshold for admittance.

Telle et al (13) reports on all COVID-19 test positive persons in Norway (January 1. -June 2020, n = 8569), studying whether age, sex, comorbidity, continent or country of birth and nursing home residency were risk factors for hospitalisation. Underlying comorbidity was proxied by hospital-based in- or outpatient treatment during the two months before the SARS-CoV-2 test. Multivariable generalised linear models were used to estimate risk ratios (RRs). Risk of hospitalisation was particularly high for the elderly (for those aged 90 and above: RR 9.5; 95% CI 7.1–12.7; comparison group aged below 50), Norwegian residents born in Asia, Africa or Latin-America (RR 2.1; 95% CI 1.9–2.4; comparator born in Norway), patients with underlying comorbidity (RR 1.6; 95% CI 1.4–1.8) and men (RR 1.3; 95% CI 1.2–1.5).

The authors point out that as their study was registry based, they lack important information on potential causes and confounders, in particular on specific comorbidities.

Across the studies, trends are apparent. However, due to the heterogeneity between studies in relation to study designs, risk factor definitions, data analysis and –reporting, we stress that there are uncertainties in direct comparisons of results between included studies.
Four studies showed a clear dose response relationship between increasing age and risk of hospital admission (7, 8, 10, 13). Four studies reported an increased risk for hospital admission in men and for people overweight and obese (7, 8, 10, 14). Based on three studies, the majority of non-whites or foreign born were at increased risk of admission. Five studies (6-8, 10, 14). provided a granular overview of adjusted HRs/ORs for a broad selection of comorbidities, conditions and ongoing treatments. Most of these were associated with a greater risk for admission, with apparent increases in risk based on severity of condition. Two studies (8, 14) reported increasing risk by number of co-existing comorbidities. Severe kidney disease, diabetes, ongoing chemotherapy, severe immunodeficiency, heart failure, organ transplantation and Down syndrome stand out with a greater associated risk of hospital admission (OR/HR >=3).

Table 3. Studies assessing risk factors predicting hospitalisation related to COVID-19; overview of reported findings by author, significant values greater-than-or-equal 3 are marked red, values greater-than-or-equal 2 are marked orange, all significant findings below 2 are bold black. Non-significant findings are one font size smaller. Telle et al. is not listed below, due to limited number of variables reported.

Author	**Bergman**	**Burn**	**Clift**		**Petrilli**	**Reilev**
Country	Sweden	Spain	England		US	Denmark
Study period	Jan – Sep, 2020	Mar – May, 2020	Jan -Apr, 2020		Mar -Apr, 2020	Feb – May, 2020
Study sample	All Swedes	5,586,521	6,083,102		11,544	410,697
COVID-19 admitted	13,589	16,901	10,776		2,741	11,122
Testing method	mixed	PCR, Diagnosis	PCR		PCR	PCR
Statistic	Adjusted odds ratio (95% CI)	Adjusted hazard ratio (95 % CI)	Adjusted hazard ratio (95 % CI)		Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Target population	General population	General population	General population		COVID positive individuals	COVID positive individuals
Participants sex	mixed	mixed	men	women	mixed	mixed
Age						
0-19	reference					
19- 44					reference	
20-29	**OR 2.45 (1.69–3.55)**					
20-39						**OR 0.4 (0.3–0.5)[1]**
30-39	**OR 4.12 (2.86–5.93)**					
40-49	**OR 7.25 (5.05–10.41)**					**OR 0.6 (0.5–0.8)[1]**
50-59	**OR 10.17 (7.09–14.60)**					reference
45-54					**OR 2.14 (1.76 to 2.59)*** **	
60-69	**OR 8.46 (5.89–12.14)**					**OR 1.6 (1.3–1.9)[1]**
55-64					**OR 3.67 (3.01 to 4.48)*** **	
70-79	**OR 7.31 (5.08–10.50)**					**OR 4.7 (3.9–5.7)[1]**
65-74					**OR 8.7 (8.77 to 11.22)*** **	
> 75					**OR 37.87 (26.1 to 56.03)*** **	
80-89	**OR 9.16 (6.36–13.19)**					**OR 4.8 (3.9–5.8)[1]**
> 90	**OR 10.17 (7.02–14.75)**					**OR 3.5 (2.6–4.7)[1]**
Sex						
male	**OR 1.59 (1.53–1.65)**				**OR 2.76 (2.39 to 3.2)*** **	**OR 1.8 (1.6–2.0)[1]**
Race/ ethnicity						
non-Hispanic white			reference		reference	
non-Hispanic African American					OR 0.81 (0.65 to 1.01)	
Asian					OR 1.29 (0.97 to 1.72)	
Blacks			**HR 2.59 (2.27 to 2.97)**	**HR 2.30 (1.97 to 2.68)**		
Indian			**HR 2.15 (1.89 to 2.44)**	**HR 1.89 (1.60 to 2.24)**		
Chinese			**HR 1.51 (1.03 to 2.20)**	HR 1.15 (0.71 to 1.85)		
Pakistani			**HR 2.01 (1.72 to 2.36)**	**HR 1.52 (1.21 to 1.89)**		
Bangladeshi:			**HR 1.71 (1.41 to 2.08)**	**HR 1.41 (1.11 to 1.79)**		
Asian (other)			**HR 2.29 (1.91 to 2.74)**	**HR 2.14 (1.74 to 2.64)**		
Hispanic					**OR 1.63 (1.35 to 1.97)*** **	
other/multiracial			**HR: 2.12 (1.83 to 2.46)**	**HR 1.90 (1.64 to 2.21)**	**OR 1.6 (1.21 to 2.11)*** **	
unknown					OR 0.89 (0.65 to 1.23)	
Comorbidities						
0 comorbidity						reference
1 comorbidity						**OR 1.7 (1.5–2.0)[2]**
2 comorbidities						**OR 2.1 (1.8–2.5)[2]**
3 comorbidities						**OR 3.1 (2.5–3.8)[2]**
4+ comorbidities						**OR 3.9 (3.2–4.8)[2]**
Cardiovascular						
Heart failure			**HR 1.33 (1.21 to 1.46)**	**HR 1.38 (1.23 to 1.55)**	**OR 4.43 (2.59 to 8.04)*** **	**OR 2.6 (2.0–3.4)[2]**
CAD /CHD /IHD	**OR 1.08 (1.02–1.14)**	**HR 1.43 (1.36 to 1.51)**	HR 1.06 (0.99 to 1.14)	**HR 1.11 (1.02 to 1.22)**	OR 1.08 (0.81 to 1.44) .	**OR 1.4 (1.2–1.7)[2]**
Atrial fibrillation			**HR 1.19 (1.10 to 1.29)**	**HR 1.34 (1.22 to 1.47)**		**OR 1.4 (1.2–1.7)[2]**
Thrombo-embolism			**HR 1.30 (1.17 to 1.44)**	**HR 1.34 (1.21 to 1.50)**		
Peripheral vascular disease			**HR 1.27 (1.13 to 1.42)**	**HR 1.21 (1.03 to 1.44)**		
Congenital heart disease			HR 0.97 (0.75 to 1.25)	HR 0.97 (0.75 to 1.25)		
Hypertension	**OR 1.24 (1.18–1.31)**	**HR 1.11 (1.06 to 1.17)**			**OR 1.78 (1.49 to 2.12)*** **	**OR 1.7 (1.5–1.9)[2]**

Stroke			HR 1.31 (1.20 to 1.42)	HR 1.39 (1.27 to 1.53)		OR 1.3 (1.1–1.6)[2]
Hyperlipidaemia		HR 1.17 (1.10 to 1.24)			OR 0.62 (0.52 to 0.74)	
Kidney						
chronic kidney disease/ Hospital-diagnosed kidney disease	OR 1.47 (1.36–1.60)	HR 1.51 (1.41 to 1.60)			OR 2.60 (1.89 to 3.61)***	OR 2.9 (2.2–3.9)[2]
Glomerular disease	OR 1.20 (1.00–1.43)					
Chronic kidney disease stage 3			HR 1.28 (1.19 to 1.38)	HR 1.35 (1.25 to 1.46)		
Chronic kidney disease stage 4			HR 2.00 (1.67 to 2.39)	HR 1.79 (1.48 to 2.17)		
Chronic kidney disease stage 5			HR 3.86 (3.25 to 4.58)	HR 4.17 (3.39 to 5.12)		
Chronic kidney disease stage 5 with dialysis			HR 5.90 (4.22 to 8.25)	HR 3.72 (2.06 to 6.75)		
Chronic kidney disease stage 5 with transplant			HR 7.09 (5.30 to 9.47)	HR 5.54 (3.55 to 8.67)		
Liver						
Chronic liver disease	OR 1.07 (0.93–1.23)					OR 2.3 (1.6–3.3)[2]
Cirrhosis of the liver			HR: 1.88 (1.46 to 2.41)	HR 1.83 (1.35 to 2.49)		
Pulmonary						
Pulmonary disease (chronic obstructive pulmonary disease or asthma)					OR 1.08 (0.88 to 1.33)	OR 1.8 (1.5–2.1)[2]
COPD	OR 1.37 (1.28–1.47)	HR 1.50 (1.39 to 1.63)	HR 1.36 (1.25 to 1.49)	HR 1.34 (1.21 to 1.49)		
Asthma	OR 1.22 (1.13–1.31)		HR 1.10 (1.02 to 1.19)	HR 1.12 (1.04 to 1.21)		
Rare lung conditions (bronchiectasis, cystic fibrosis, or alveolitis)			HR 1.28 (1.06 to 1.55)	HR 1.28 (1.06 to 1.55)		
Pulmonary hypertension or pulmonary fibrosis			HR 1.56 (1.12 to 2.17)	HR 1.56 (1.12 to 2.17)		
Endocrine						
Diabetes	OR 1.54 (1.46–1.62)				OR 2.24 (1.84 to 2.73)***	OR 1.8 (1.6–2.2)[2]
DM1			HR: 3.66 (2.90 to 4.62)	HR 4.03 (3.12 to 5.22)		
DM2		HR 4.47 (4.02 to 4.98)	HR: 2.57 (2.27 to 2.91)	HR 2.64 (2.27 to 3.07)		
Any insulin use						OR 2.3 (1.7–3.0)[2]
Non-insulin glucose-lowering-drug use						OR 1.7 (1.4–2.1)[2]
Insulin monotherapy use						OR 2.4 (1.5–3.6)[2]
Neurological, mental						
Dementia	OR 1.09 (0.99–1.20)	HR 1.86 (1.68 to 2.06)	HR: 2.12 (1.92 to 2.34)	HR 1.73 (1.56 to 1.92)		OR 0.5 (0.4–0.7)[2]
Severe mental illness (F20, F25, F29, F30, severe depression)			HR: 1.28 (1.19 to 1.38)	HR 1.37 (1.28 to 1.47)		
Major psychiatric disorder (F20 F25 F30 F31)						OR 2.1 (1.2–3.7)[2]
Major psychiatric disorder, Benzodiazepines and derivate use						OR 1.7 (1.4–2.1)[2]
Major psychiatric disorder, Antipsychotic use						OR 1.5 (1.1–1.9)[2]
Major psychiatric disorder, Antidepressant use						OR 1.3 (1.1–1.5)[2]
Motor neurone disease, multiple sclerosis, myasthenia gravis, or Huntington's			HR 2.47 (1.90 to 3.22)	HR 2.47 (1.90 to 3.22)		
Cerebral palsy			HR 2.66 (1.42 to 4.98)	HR 2.66 (1.42 to 4.98)		
Epilepsy			HR 1.57 (1.33 to 1.86)	HR 1.57 (1.33 to 1.86)		
Parkinson			HR 1.70 (1.32 to 2.18)	HR 1.70 (1.32 to 2.18)		
No learning disability			ref			
Learning disability apart from Down's Syndrome			HR 1.38 (1.22 to 1.56)	HR 1.53 (1.34 to 1.76)		
Down's syndrome	OR 3.24 (1.55–6.78)		HR 4.36 (2.39 to 7.94)	HR 4.36 (2.39 to 7.94)		
Other						
Organ transplantation	OR 1.41 (1.07–1.84)					OR 3.4 (1.7–6.6)[2]
Solid organ transplant (excluding kidney and bone marrow)			HR 2.02 (1.27 to 3.21)	HR 1.57 (0.80 to 3.05)		
Autoimmune condition		HR 1.33 (1.24 to 1.43)				
Rheumatoid arthritis						OR 1.5 (1.1–1.9)[2]
Rheumatoid arthritis or SLE (Lupus)			HR 1.30 (1.07 to 1.57)	HR 1.35 (1.17 to 1.56)		
Malignancy	OR 1.01 (0.96–1.07)	HR 1.24 (1.17 to 1.32)			OR 0.88 (0.65 to 1.19)	OR 1.4 (1.2–1.6)[2]
Blood cancer			HR 1.29 (1.05 to 1.57)	HR 1.40 (1.10 to 1.78)		
Respiratory tract cancer			HR 1.44 (1.14 to 1.83)	HR 1.65 (1.25 to 2.17)		
Not on chemotherapy in last 12 months			reference	reference		
Chemotherapy grade A			HR 1.72 (1.24 to 2.37)	HR 2.11 (1.48 to 3.01)		
Chemotherapy grade B			HR 3.64 (2.95 to 4.49)	HR 4.19 (3.28 to 5.37)		

Chemotherapy grade C			**HR 4.11 (2.20 to 7.68)**	**HR 15.53 (8.36 to 28.85)**		
Sickle cell disease or severe immunodeficiency	**OR 1.33 (1.01 to 1.73)**		**HR 4.87 (2.67 to 8.87)**	**HR 6.68 (4.06 to 10.97)**		
HIV/AIDS	OR 1.13 (0.76–1.68)					
Oral steroids 4+ scripts in past 6 months			**HR 1.42 (1.25 to 1.62)**	**HR 1.92 (1.71 to 2.17)**		
BMI						
< 25		**HR 1.78 (1.70 to 1.87)**			reference	
> 25 / 25 - 29.9 (Overweight)					**OR 1.3 (1.07 to 1.57)****	
> 30					**OR 1.8 (1.47 to 2.2)*****	**OR 2.1 (1.8–2.5)²** (Based on ICD code for overweight)
>40 / ≥40 (Obese class III)					**OR 2.45 (1.78 to 3.36)*****	
unknown					**OR 0.47 (0.31 to 0.69)*****	
Charlson Comorbidity Index						
Charlson 1		**HR 1.45 (1.35 to 1.56)**				
Charlson 2		**HR 1.63 (1.53 to 1.74)**				
Charlson 3		**HR 2.33 (2.18 to 2.48)**				
Smoking/ Substance abuse						
Never smoker					reference	
Current smoker					**OR 0.59 (0.43 to 0.81)****	
Former smoker					**OR 0.69 (0.56 to 0.85)*****	
Unknown smoking status					**OR 1.43 (1.16 to 1.75)*****	
Alcohol abuse	OR 0.76 (0.69–0.84)					**OR 1.7 (1.3–2.3)²**
Substance abuse						OR 1.3 (0.9–1.9)²
Explanatory information	Adjusted for all variables in the above column	Adjusted for age,sex and comorbities	Adjusted for variables shown, deprivation, and fractional polynomial terms for body mass index (BMI) and age. Model includes fractional polynomial terms for age (3 3) and BMI (0.5 0.5 ln (BMI)) and interaction terms between age terms and type 2 diabetes.		Pvalue: *** = p<0.001; ** = p<0.01,* = p<0.05; Adjusted for Age at time of testing, sex, ethnicity, hypertension, hyperlipidemia, coronary artery disease, heart failure, pulmonary disease, malignancy, diabetes, obesity	¹ = Age-, sex- and number of comorbidities adjusted OR (95% CI), table 4 in supplementary files of original study; ² = Age and sex-adjusted OR (95% CI);

Risk factors for severe/critical disease, including ICU admission, related to COVID-19

Brief summary: Four studies assessed risk factors for ICU admissions due to COVID-19 (10, 11, 13, 14). Two studies provided a detailed overview of comorbidities and demographic factors (10, 11), and two studies presented mainly demographic factors (8, 13). Overall, increasing age, male sex, chronic kidney disease, immune disorders, asthma, diabetes and Down syndrome were associated with increased risk for severe disease. Decreasing risk for ICU admission in the last decades of life may rather reflect differing treatment approaches than severity of disease.

Bergman et al (10) conducted a nationwide, registry-based study to investigate potential risk factors for diagnosis, hospitalisation, and mortality. The study population comprised all COVID-19 cases confirmed in Sweden by mid-September 2020 and 434,081 randomly sampled general population controls. Of the COVID-19 cases 13,589 (15.6%) had been non-ICU hospitalised for confirmed COVID-19 and 2,494 (2.9%) had been ICU hospitalised. Older age was the strongest risk factor for ICU-admission, while children and under 20s had the lowest risk for ICU-admission. Approximately 90% of ICU and non-ICU hospitalised patients had at least one of the investigated comorbidities or medications, and this was associated with more than twice the odds of ICU and non-ICU hospitalisation after adjustment for demographic factors. The two comorbidities most strongly associated with ICU and non-ICU hospitalisation after adjustment for other risk factors were diabetes and Down syndrome. Cancer in the past year, was associated with COVID-19 diagnosis and admission, but not with ICU hospitalisation, after adjustment for all variables.

Lee et al (11) conducted a retrospective nationwide population study, they investigated the data of 7,339 laboratory-confirmed COVID-19 patients, aged 18 years and older, using the Korean Health Insurance Review and Assessment (HIRA) Service database, covering 98% of the Korean population. Comorbidities and medications used were identified using HIRA codes, and severe COVID-19 was defined as that requiring oxygen therapy, a mechanical ventilator, cardiopulmonary resuscitation, or extracorporeal membrane oxygenation. Mean patient age was 47.1 years; 2,970 (40.1%) patients were male. After adjusting for confounding factors, diabetes mellitus, chronic kidney disease, previous history of pneumonia, aging, and male sex were significantly associated with increased risk of severe disease.

Reilev et al (8) report on characteristics of ICU admissions in a nationwide cohort comprising 11,122 confirmed COVID-19 cases in Denmark in the period February 7th, 2020 until May 19th, 2020. Compared to non-ICU participants, ICU admitted participants (2.8%) were comprised of a higher ratio of men (73%) to women (27%) (non-ICU: men (51%), women (49%)) and were slightly younger (median 68 (interquartile range(IQR) 58–75)) (non-ICU: median 72 (IQR 55–81)). Compared to fatal cases (5.2%), non-fatal cases admitted to the ICU were younger and presented with fewer comorbidities. The authors argue this might be due to ICU prioritisation of patients with better outcome prospects if provided with intensive care treatment, for example ventilation.

Telle et al (13) reported on all COVID-19 test positive persons in Norway by end of June 2020 (n = 8569), studying whether age, sex, comorbidity and continent of birth were risk factors for invasive mechanical ventilation treatment. Multivariable generalised linear models were used to assess risk

ratios. Age stood out as the most relevant risk factor. Underlying comorbidity was proxied by hospital-based in- or outpatient treatment during the two months before the SARS-CoV-2 test and did not present as a risk factor. Men (RR 2.8 (95% CI 1.9–4.1) and residents born in Africa, Asia and Latin-America (RR 2.7 (95%CI 1.9–3.8)) were at higher risk of receiving ventilation treatment. Nursing home residents had a lower RR for mechanical ventilation, although this needs to be seen in light of that the Norwegian health authorities recommend nursing home patients with COVID-19 not to be admitted to hospital but managed within the nursing home setting.

The authors point out that as their study was registry based, they lack important information on potential causes and confounders, in particular on specific comorbidities.

Table 4. Studies assessing risk factors predicting development of severe disease due to COVID-19; overview of reported findings by author, significant values greater-than-or-equal 3 are marked red, values greater-than-or-equal 2 are marked orange, all significant findings below 2 are bold black. Non-significant findings are one font size smaller. Telle et al. is not listed below, due to limited number of variables reported. Reilev et al. is not listed as they did not report OR/HR/RR.

Author	**Bergman**	**Lee**
Country	Sweden	South Korea
Study period	Jan – Sep, 2020	Jan – May, 2020
Study sample	All Swedes (excluding care home residents, positive cases prior to start)	7339 lab-confirmed adult COVID-19 patients, Insurance database.
Testing method	Diagnosis or positive test	PCR
COVID-19 admitted	13,589	Unclear
Statistic	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Target population	General population	COVID positive
Participants sex	mixed	mixed
Age		
0-19	reference	
20-29	**OR 3.62 (1.45–9.02)**	
30-39	**OR 3.70 (1.49–9.21)**	
40-49	**OR 9.68 (3.94–23.77)**	
50-59	**OR 20.30 (8.30–49.64)**	
60-69	**OR 23.97 (9.80–58.62)**	
70-79	**OR 14.59 (5.94–35.81)**	
80-89	**OR 5.42 (2.17–13.57)**	
>90	OR 0.84 (0.22–3.19)	
Male sex	**OR 3.04 (2.76–3.35)**	
Comorbitities		
Coronary artery/Cardiovascular disease	**OR 0.74 (0.65–0.85)**	
Heart disease		OR 1.09 (0.84–1.40)
Hypertension	**OR 1.42 (1.27–1.58)**	OR 0.99 (0.82–1.20)
Diabetes	**OR 1.82 (1.62–2.03)**	**OR 1.42 (1.16–1.74)**
COPD	OR 1.12 (0.94–1.34)	OR 1.16 (0.67–2.00)
Asthma	**OR 1.53 (1.30–1.79)**	**OR 1.40 (1.03–1.91)**
Tuberculosis		**OR 3.06 (1.18–7.94)**
Chronic kidney disease	OR 1.18 (0.95–1.46)	**OR 3.55 (1.75–7.18)**
Glomerular disease	OR 1.40 (0.97–2.02)	
Liver disease	**OR 1.37 (1.05–1.79)**	OR 0.97 (0.74–1.27)
Dementia/Alzheimer	**OR 0.15 (0.07–0.31)**	
Down Syndrome	**OR 4.26 (1.01–17.90)**	
HIV/AIDS	OR 1.45 (0.73–2.89)	OR 8.60 (0.71–103.83)
Solid organ transplantation	OR 1.36 (0.82–2.26)	
Immune disorder	**OR 1.79 (1.04–3.09)**	
Autoimmune disorder	OR 0.95 (0.80–1.14)	
Cancer	**OR 0.81 (0.71–0.93)**	OR 1.30 (0.86–1.95)
Smoking/ Substance abuse		
Alcohol intoxication	**OR 0.80 (0.66- 0.97)**	
	[I]Definition: ICU intensive care unit Adjusted for all variables in the above column	Included one medication at a time with all variables regarding comorbidities and significant variables in the univariable analyses and one comorbidity at a time with all variables regarding medications and significant variables in the univariable analyses

Risk factors for COVID-19-related death

Brief summary: Nine studies assessed risk factors for COVID-19-related death (5, 6, 8-14). Eight studies provided a granular overview of predicting factors, while one study presented mainly demographic factors (13). Results are summarised side by side in Table 5. Overall, increasing age was found to be the strongest predictor of COVID-19-related death. Furthermore, male sex, ethnicity, most comorbidities, increasing severity and number of comorbidities were found to be significant predictors of COVID-19-related death.

Barron et al (5) performed a whole-population study assessing risk factors for COVID-19 related in-hospital death between March 1st and May 11th, 2020. The authors included 61,414,470 individuals registered with a general practice in England who were alive on February 16th, 2020. They used multivariable logistic regression to examine the effect of diabetes status, by type, on in-hospital COVID-19-related death, adjusting for demographic factors and cardiovascular comorbidities. 0.4% had a recorded diagnosis of type 1 diabetes, 4.7% type 2 diabetes and 0.1% another types of diabetes. 23,698 COVID-19-related in-hospital deaths occurred during the study period, where 7,434 deaths, about one third, occurred in people with type 2 diabetes, 364 with type 1 diabetes, and 69 in people with other types of diabetes. Adjusted for age, sex, index of multiple deprivation, ethnicity and region, the OR for death in people with type 1 diabetes was 3.51 (95% CI 3.16–3.90) and for people with type 2 diabetes 2.03 (1.97–2.09) compared with the population without known diabetes. A limitation with this study is that the registration of death was limited to in-hospital occurrences only. The authors were also limited in their ability to adjust for other comorbidities because of limitations in the datasets used and which were available.

Bergman et al (10) conducted a nationwide, registry-based study to investigate potential risk factors for death. The study population comprised all COVID-19 cases confirmed in Sweden by mid-September 2020 and 434,081 randomly sampled general population controls. 6,566 COVID-19 related deaths were registered. The strongest predictor for all-cause mortality in cases vs general population controls was age, with a clear dose response relationship, with a hazard ratio for death being 13.7 times greater for age group 60-69 compared to the reference group (0-19), and the hazard ratio for death for those 90 years old and above being 90 times greater than the reference group. Children and adults below 40 years of age had the lowest hazard ratios. Increased risk was also observed for people with Down syndrome, male sex, organ transplantation and dementia. The authors point out that the presence of some medical conditions, especially mild conditions, may be underestimated because complete histories of medical conditions were not available.

Burn et al (14) used patient-level data to estimate risk of death after being diagnosed with COVID-19 in Catalonia, Spain. Of the 102,002 that were diagnosed with COVID-19, 5,273 died between March 1st and May 6th, 2020. Cause-specific Cox models were estimated for comorbidities separately, adjusting for age and sex. Models with age as risk factor, were adjusted for gender and comorbidities. Increasing age was reported as the strongest risk factor, with the oldest age group having highest risk (95 years, HR 23.6 (20.52-27.16), with higher risk found for women (HR 36.03 (29.71 to 43.69)) compared to men (HR 16.20 (12.94 to 20.28)). For comorbidities, higher risk was found for dementia and multimorbidity (3+) among those over 70 years of age. For participants

below 70 years, higher risk was found for most comorbidities, compared to those over 70, with higher risk seen for most comorbidities for women below 70 compared to men below 70.

The data for this study was collected during the first wave in Spain, during which the health care system may have been overburdened. Effective treatment options were still uncertain, indicating that the estimated risks for this study sample might be overinflated compared to the current risk, with better health care capacity and known effective treatment options.

Clift et al (6) report on characteristics related to COVID-19 related death in a nationwide cohort comprising 1,205 general practices in England with linkage to COVID-19 test results, Hospital Episode Statistics, and death registry data. The practices were randomly assigned to a derivation dataset and to a validation cohort. The validation cohort provided a basis for two calibrations of the risk models over different periods. The results in detail, based on 4,384 deaths of the derivation cohort, are presented by sex in Table 5. Their primary outcome was time to death from COVID-19 (either in hospital or outside hospital), defined as confirmed or suspected death from COVID-19 as per the death certification or death occurring in an individual with confirmed SARS-CoV-2 infection at any time in the period January 24th to April 30th 2020. They report increased risk for all non-white males, and most of the investigated comorbidities. Interestingly, the adjusted hazard ratios for body mass index, age, and the interaction between age and type 2 diabetes for COVID-19 related deaths were higher for younger age groups. The highest risk was identified in individuals with Down syndrome, with a HR of 2.55 (18.13-58.42) in women and HR 9.80 (4.62-20.78) in men.

The authors point out that no systematic community testing was performed and that only those unwell enough to attend hospital were tested. This, they conclude would overestimate risks of severe outcomes in those who tested positive. Also, as the outcome included death suspected to be caused by COVID-19, it is uncertain whether COVID-19 was the main cause of death.

Hernandez-Vasquez et al (12) reported on risk factors for death from COVID-19 in 51,053 COVID-19 cases in Mexico. Data were collected from the publicly available Mexican epidemiological surveillance system which collects demographic and clinical information related to COVID-19 cases. Logistic regression was used to estimate the associations between possible risk factors and death, and the probabilities of death was estimated across age groups based on the number of comorbidities. High blood pressure, diabetes, obesity, immunosuppression, other CVDs, COPD, and chronic kidney disease were associated with an increased risk of death, as were increasing numbers of comorbidities. Incremental increases in risk of death was found for increasing age for both men and women. The authors report detailed analysis stratified by age and sex in their supplementary data.

Lee et al (11) conducted a retrospective nationwide population study and reported risk factors for death for 7,339 adult COVID-19 cases in South Korea using the Korean Health Insurance Review and Assessment Service (HIRA) database. Comorbidities and medications used were identified using HIRA codes. Mean patient age was 47.1 years and 2,970 (40.1%) cases were male. In fully adjusted models, increased risk of death was observed for diabetes (OR 2.21 (1.59–3.08)), chronic kidney disease, (OR 3.21 (1.35–7.63)) and male sex (OR 2.10 (1.51–2.92)). Incremental increases in risk of death was found for increasing age.

Reilev et al (8) investigated risk factors for COVID-19 related death in a nationwide cohort comprising 11,122 confirmed COVID-19 cases in Denmark in the period February 7th, 2020 until May 19th, 2020. During this period there were 577 COVID-19-related deaths registered. They report a mortality rate of below 5% for persons under 80 years of age without any comorbidities, while almost 4 out of 5 fatal cases had two or more comorbidities. The strongest predictor for death was age, with a clear dose response relationship, with odds of death being 4.4 times greater for age group 60-69 compared to the reference group (50-59), and the odds of death for those 90 years old and above being 90 times greater than the reference group. Weaker, but still significant, findings were reported for male sex (OR 2.1 (1.7–2.6)), dementia (OR 1.7 (1.3-2.2) and major psychiatric disorder (ORs from 1.5 to 3).

Telle et al (13) reports on risk factors for death all COVID-19 test positive persons in Norway by the end of June 2020 (n = 8,569). Hospital-based in- or outpatient treatment during the two months before administration of PCR test was used as proxy for underlying comorbidity. Multivariable generalised linear models were used to estimate risk. Men (RR 1.7; 95% CI 1.4–2.1) and residents born in Africa, Asia and Latin-America (RR 2.3; 95% CI 1.5–3.5) were at higher risk of dying, but the risk was especially high for the elderly (for those aged 90 and above: RR 607.9; 95% CI 145.5–2540.1; comparison group aged below 50) and residents in nursing homes (RR 4.2; 95% CI 3.1–5.7).

The authors point out that as their study was registry based, they lack important information on potential causes and confounders, in particular on specific comorbidities. As hospital-based treatment two months prior to PCR test was use as proxy for comorbidity, there is imprecision related to this measure.

Williamson et al (9) investigated risk factors for COVID-19-related death in a retrospective registry study of 17 278 392 adults in the UK. 10 926 COVID-19-related deaths where included, Highest risks were found for high age (70-79: HR 6.07 (5.51–6.69), >80: HR 20.60 (18.70–22.68)), people with organ transplantation (HR 3.53 (2.77–4.49)), blood cancer diagnosed less than one year ago (HR 2.80 (2.08–3.78), neurological disorders (HR 2.58 (2.38–2.79) and kidney disease (HR 2.52 (2.33–2.72)). Increased risk was also seen for male sex (HR 1.59 (1.53–1.65)), ethnicities other than white (HR 1.3-1.5), people with diabetes (HR 1.90 (1.72–2.09)), chronic liver disease (HR 1.75 (1.51–2.03)), obesity (BMI 35-39.9 HR 1.40 (1.30-1.52), BMI $\geq$40 HR 1.92 (1.72–2.13)) and high deprivation score (HR 1.79 (1.68–1.91) for most deprived). The authors found a lower risk associated with current smoking status (HR 0.89 (0.82–0.97)), but the association was found to be largely driven by chronic respiratory disease, of which smoking is a key risk factor. The authors highlight that these findings need to be evaluated with caution. For more details on reported results, see Table 5.

Across the studies, trends are apparent. All studies assessing age as a predictor found it to be a consistent and strong risk factor for COVID-19-related death with a steep and continuous increase in risk with increasing age. Male sex and ethnicity other than white was also consistently, but more modestly, associated with increased risk of death. Two studies (5, 9) found increasing risk of death with increasing degree of deprivation (measure by Indices of multiple deprivation (IMD)). Most medical risk factors investigated were associated with higher risk of death, with increasing numbers and severity of comorbidities increasing the risk for death further. Chronic kidney

disease, diabetes, dementia, ongoing chemotherapy, organ transplantation, severe immunodeficiency, major psychiatric disorder with antipsychotic treatment, cerebral palsy and Down syndrome were associated with the highest risk of death (OR/HR >=3). Results reported for obesity were mixed. These trends need to be interpreted with caution due to heterogeneity in study designs, selected predicting factors, data analysis and data reporting.

Table 5. Studies assessing risk factors predicting COVID-19-related death; overview of reported findings by author, significant values greater-than-or-equal 3 are marked red, values greater-than-or-equal 2 are marked orange, all significant findings below 2 are bold black. Non-significant findings are one font size smaller. Telle et al. is not listed below, due to limited number of variables reported.

Author	Barron	Bergman	Burn	Clift		Hernandez-Vasquez	Lee	Reilev	Williamson
Country	England	Sweden	Spain	England		Mexico	South Korea	Denmark	UK
Study period	Feb – May, 2020	Jan – Sep, 2020	Mar – May, 2020	Jan -Apr, 2020		Feb – May, 2020	Jan – May, 2020	Feb – May, 2020	Feb -May, 2020
Study sample	61,414,470	All Swedes	5,586,521	6,083102		51,053	7,339	410,697	17,278,392
Testing method	Pos. test or COVID-19 registered death	Diagnosis or positive test	PCR, Diagnosis	PCR		PCR	PCR	PCR	ICD U071 or U072
COVID-19 admitted	Unclear	13,589	16,901	10,776		Unclear	Unclear	11,122	Unclear
COVID-19 deaths	23698 in-hospital	6,566	5,273	4,384		5,233	227	577	10,926
Statistic	Adjusted odds ratio (95 % CI)	Adjusted odds ratio (95% CI)	Adjusted hazard ratio (95 % CI)	Adjusted hazard ratio (95 % CI)		Adjusted odds ratio (95 % CI)	Adjusted odds ratio (95 % CI)	Adjusted odds ratio (95 % CI)	Adjusted hazard ratio (95 % CI)
Target population	COVID positive	General Population	COVID positive	General Population		COVID positive	COVID positive	COVID positive	General Population
Participant sex	mixed	mixed	mixed	men	women	mixed	mixed	mixed	mixed
Age									
Age, continuous									**OR 1.12 (1.11–1.14)[1]**
0-19		reference							
0-39	**OR 0.01 (0.01–0.01)**								
20-29		HR 0.52 (0.17–1.62)	**0.01 (0.004-0.025)** (25y)						
18-39								**HR 0.06 (0.04–0.08)**	
30-39		HR 0.62 (0.21–1.88)							
40-49	**OR 0.11 (0.10–0.12)**	**HR 2.18 (0.79–6.00)**						**HR 0.30 (0.25–0.36)**	
50-59	**OR 0.36 (0.34–0.39)**	**HR 5.33 (1.98–14.37)**					reference	reference	
60-69	reference	**HR 13.70 (5.10–36.8)**	reference (65y)				**OR 4.4 (2.5–7.9)[2]**	**HR 2.40 (2.16–2.66)**	
70-79	**OR 2.64 (2.53–2.76)**	**HR 36.27 (13.5–97.2)**	**HR 3.62 (3 - 4)** (75y)				**OR 15.2 (8.7–26)[2]**	**HR 6.07 (5.51–6.69)**	
>80	**OR 9.20 (8.83–9.58)**							**HR 20.60 (19–23)**	
80-89		**HR 67.65 (25.2–181)**	**HR 9.38 (9 - 10)** (85y)				**OR 29.9 (17–52)[2]**		
> 90		**HR 93.13 (34.7–250)**	**HR 23.60 (21 -27)** (95y)				**OR 90.2 (50–162)[2]**		
Sex									
male	**OR 1.94 (1.89–1.99)**	**HR 1.67 (1.59–1.76)**					**OR 2.1 (1.7–2.6)[2]**	**HR 1.59 (1.53–1.65)**	**OR 2.10 (1.51–2.92)[1]**
Number of comorbidities									
0			reference			reference	reference		
1			**HR 2.45 (2.13 to 2.81)[1]**			**OR 1.89 (1.75, 2.04)**	**OR 2.6 (1.6–4.0)[2]**		
2			**HR 1.68 (1.46 to 1.94)[1]**			**OR 2.51 (2.30, 2.73)**	**OR 2.6 (1.7–4.1)[2]**		
3							**OR 3.5 (2.2–5.4)[2]**		
3+			**HR 2.59 (2.28 to 2.94)[1]**			**OR 3.49 (3.15, 3.86)**			
4+							**OR 5.2 (3.4–8.0)[2]**		
Income/ multiple deprivation quintiles									
1	**OR 1.88 (1.80–1.96)**	**HR 0.67 (0.59–0.74)**						**HR 1.79 (1.68–1.91)**	
2	**OR 1.53 (1.47–1.60)**	**HR 0.71 (0.64–0.79)**						**HR 1.51 (1.42–1.61)**	
3	**OR 1.25 (1.20–1.31)**	**HR 0.79 (0.73–0.85)**						**HR 1.22 (1.15–1.30)**	
4	**OR 1.14 (1.09–1.19)**	**HR 0.88 (0.83–0.93)**						**HR 1.12 (1.05–1.19)**	
5 (least deprived)	reference	reference						reference	
Race/ ethnicity									
non-Hispanic white	reference			reference	reference			reference	
Black	**OR 1.71 (1.61–1.82)**			**HR 3.03 (2.42-3.80)**	**HR 1.98 (1.39-2.83)**			**HR 1.48 (1.29–1.69)**	
Asian	**OR 1.35 (1.28–1.42)**							**HR 1.45 (1.32–1.58)**	
Indian				**HR 1.59 (1.25-2.01)**	**HR 1.89 (1.43-2.51)**				
Chinese				**HR 2.47 (1.49-4.09)**	HR 1.21 (0.51-2.90)				
Pakistani				**HR 1.84 (1.39-2.44)**	HR 1.40 (0.91-2.14)				
Bangladeshi				**HR 2.27 (1.65-3.12)**	HR 1.41 (0.88-2.26)				
Asian (other)				**HR 2.02 (1.49-2.74)**	HR 1.19 (0.72-1.97)				
other/multiracial	**OR 1.43 (1.23–1.67)**			**HR 2.04 (1.60-2.58)**	**HR 1.73 (1.28-2.35)**			**HR 1.43 (1.11–1.84)**	
other								**HR 1.33 (1.10–1.61)**	
unknown	**OR 0.33 (0.31–0.35)**								
Cardiovascular									
Heart disease			HR 0.96 (0.88 to 1.03)						
Heart failure				**HR 1.40 (1.24-1.59)**	**HR 1.37 (1.18-1.60)**		OR 1.1 (0.8-1.5)[1]		
CAD /CHD /IHD		**HR 1.13 (1.07–1.20)**		**HR 1.13 (1.02-1.24)**	**HR 1.24 (1.10-1.40)**		OR 0.7 (0.5-0.9)[1]	**HR 1.17 (1.12–1.22)**	
Atrial fibrillation				HR 1.11 (1.00-1.24)	**HR 1.18 (1.04-1.34)**		OR 1.1 (0.8-1.4)[1]		
Thrombo-embolism				**HR 1.18 (1.01-1.38)**	**HR 1.18 (1.01-1.38)**				
Peripheral vascular disease				**HR 1.42 (1.15-1.76)**	**HR 1.42 (1.15-1.76)**				
Congenital heart disease				**HR 1.23 (0.75-2.03)**	**HR 1.23 (0.75-2.03)**				

Hypertension		**HR 1.22 (1.14–1.32)**	HR 1.01 (0.93 to 1.10)			**OR 1.67 (1.57, 1.79)**	OR 0.6 (0.5-0.8)[1]	**HR 0.89 (0.85–0.93)**	OR 0.76 (0.55–1.06)[2]
Stroke				**HR 1.24 (1.11-1.38)**	**HR 1.34 (1.19-1.51)**		OR 1.0 (0.8-1.3)[1]		
Stroke or dementia								**HR 2.16 (2.06–2.27)**	
Other CVD than hypertension			HR 1.01 (0.91 to 1.13)			**OR 1.34 (1.17, 1.55)**			OR 0.95 (0.64–1.40)[2]
Kidney									
Chronic kidney disease		**HR 1.30 (1.22–1.39)**	**HR 1.24 (1.14 to 1.35)**			**OR 3.08 (2.70, 3.51)**	OR 1.3 (0.9-1.8)[1]		**OR 3.21 (1.35–7.63)[2]**
Glomerular disease		HR 0.87 (0.70–1.07)							
Kidney disease, eGFR 30–60								**HR 1.33 (1.28–1.40)**	
Kidney disease, eGFR < 30								**HR 2.52 (2.33–2.72)**	
Chronic kidney disease (CKD) stage 3				**HR 1.18 (1.06-1.30)**	**HR 1.30 (1.17-1.45)**				
CKD stage 4				**HR 1.83 (1.46-2.29)**	**HR 1.37 (1.05-1.80)**				
CKD stage 5				**HR 2.40 (1.83-3.15)**	**HR 3.00 (2.19-4.12)**				
CKD stage 5 with dialysis				HR 2.68 (0.86-8.36)	**HR 3.67 (2.02-6.66)**				
CKD stage 5 with transplant				**HR 3.20 (1.62-6.33)**	**HR 7.84 (3.38-18.17)**				
Spleen									
Asplenia								HR 1.34 (0.98–1.83)	
Liver									
Chronic liver disease		**HR 1.27 (1.09–1.46)**					OR 1.2 (0.7-2.3)[1]	**HR 1.75 (1.51–2.03)**	OR 1.01 (0.58–1.74)[2]
Cirrhosis of the liver				HR 1.29 (0.83-2.02)	**HR 1.85 (1.15 - 2.99)**				
Pulmonary									
Pulmonary disease (COPD or asthma)							OR 1.1 (0.8-1.4)[1]		
Respiratory disease excluding asthma								**HR 1.63 (1.55–1.71)**	OR 0.83 (0.48–1.43)[2]
COPD		**HR 1.08 (1.01–1.16)**	HR 1.07 (0.94 to 1.22)	**HR 1.25 (1.11-1.42)**	**HR 1.50 (1.29-1.74)**	**OR 1.62 (1.40, 1.87)**			OR 1.34 (0.66–2.73)[2]
Asthma		**HR 0.85 (0.78–0.93)**		HR 1.03 (0.91-1.17)	**HR 0.84 (0.73-0.97)**	OR 1.02 (0.84, 1.23)			OR 0.83 (0.48–1.43)[2]
Asthma with no recent OCS use								HR 0.99 (0.93–1.05)	
Asthma with recent OCS use								**HR 1.13 (1.01–1.26)**	
Rare lung conditions (bronchiectasis, cystic fibrosis, or alveolitis)				HR 0.85 (0.60-1.19)	HR 0.85 (0.60-1.19)				
Pulmonary hypertension or pulmonary fibrosis				HR 1.55 (1.00 -2.40)	HR 1.55 (1.00-2.40)				
Influenza									OR 1.03 (0.49–2.18)[2]
Tuberculosis									OR 2.79 (0.71–10.89)[2]
Endocrine									
Diabetes		**HR 1.23 (1.16–1.30)**	**HR 1.42 (1.29 to 1.56)**			**OR 2.00 (1.87, 2.13)**	OR 1.1 (0.8-1.4)[1]		**OR 2.21 (1.59–3.08)[2]**
DM type 1	**OR 3.51 (3.16–3.90)**			**HR 5.84 (3.97-8.60)**	**HR 4.02 (2.07-7.82)**				
DM Type 2 (at mean age)	**OR 2.03 (1.97–2.09)**			**HR 4.74 (3.34-6.71)**	**HR 6.29 (4.08-9.70)**				
Other Diabetes	**OR 2.14 (1.69–2.71)**								
With HbA1c < 58 mmol mol								**HR 1.31 (1.24–1.37)**	
With HbA1c ≥ 58 mmol mol								**HR 1.95 (1.83–2.08)**	
With no recent HbA1c measure								**HR 1.90 (1.72–2.09)**	
DM, Non-insulin glucose lowering drugs							OR 1.0 (0.7-1.3)[1]		
Diabetes, Insulin							OR 1.3 (0.9-1.8)[1]		
Diabetes, Insulin monotherapy							OR 1.0 (0.6-1.7)[1]		
Neurological, mental									
No learning disability				reference	reference				
Learning disability (not Down's syndrome)				**HR 1.36 (1.14-1.60)**	**HR 1.36 (1.11-1.65)**				
Down's syndrome		**HR 10.91 (5.41–22.02)**		**HR 9.80 (4.62-20.78)**	**HR 32.55 (18.1-58.4)**				
Parkinsons disease				HR 1.13 (0.79-1.62)	HR 1.13 (0.79-1.62)				
Dementia		**HR 1.60 (1.50–1.70)**	**HR 2.84 (2.60 to 3.09)**	**HR 3.14 (2.81-3.50)**	**HR 2.91 (2.58-3.28)**		**OR 1.7 (1.3-2.2[1])**		
Epilepsy				**HR 1.58 (1.23-2.03)**	**HR 1.58 (1.23-2.03)**				
Motor neurone disease (MS, MG, HD)				**HR 1.99 (1.24-3.18)**	**HR 2.75 (1.83-4.12)**				
Cerebral Palsy				**HR 3.45 (1.10-10.78)**	**HR 3.45 (1.10-10.78)**				
Severe mental illness (F20, F25, F29, F30, severe depression)				**HR 1.26 (1.13-1.42)**	**HR 1.29 (1.15-1.45)**				
Major psychiatric disorder (F20 F25 F30 F31)							OR 1.9 (0.9-3.9)[1]		
Major psychiatric disorder, Benzodiazepines and derivates							**OR 1.8 (1.4-2.4)[1]**		
Major psychiatric disorder, Antipsychotics							**OR 3.0 (2.1-4.2)[1]**		

Major psychiatric disorder, Antidepressants						**OR 1.5 (1.2-1.9)**[1]		
Neurological disorders often with comp. RF (MND, MG ;MS, Parkinsons, CP etc)							**HR: 2.58 (2.38–2.79)**	
Other neurological disease							**HR 2.58 (2.38–2.79)**	
Other								
Organ transplantation	**HR 1.66 (1.19–2.32)**					OR 2.0 (0.8-5.1)[1]	**HR 3.53 (2.77–4.49)**	
Solid organ transplant (excluding kidney and bone marrow)			HR 1.46 (0.36-5.92)	HR 1.46 (0.36- 5.92)				
Immune disorder	HR 1.07 (0.77–1.48)							
Autoimmune disorder	HR 1.08 (1.00–1.16)	HR 1.12 (0.99 to 1.27)						
Rheumatoid arthritis			HR 1.02 (0.75-1.38)	**HR 1.32 (1.06-1.65)**		OR 0.9 (0.6-1.3)[1]		
Rheumatoid arthritis, lupus or psoriasis)							**HR 1.19 (1.11–1.27)**	
Sickle cell or severe immunodeficiency			**HR 4.41 (1.41-13.81)**	**HR 5.94 (1.89-18.67)**				
Other immunosuppressive condition							**HR 2.21 (1.68–2.90)**	
Oral steroids 4+ scripts in past 6 months			**HR 1.44 (1.19-1.73)**	**HR 1.83 (1.52-2.19)**				
Corticosteroids, systemic	**HR 1.11 (1.05–1.17)**							
Bone marrow or stem cell transplant in past 6 months			HR 1.58 (0.95-2.62)	HR 2.78 (0.22-34.55)				
HIV/AIDS	HR 0.80 (0.33–1.94)							**OR 101.92 (6–>999)**[2]
Cancer								
Malignancy	**HR 1.14 (1.08–1.19)**	**HR 1.13 (1.03 to 1.24)**				OR 1.0 (0.8-1.3)[1]		OR 1.21 (0.67–2.18)[2]
Cancer (non-haematological, versus none), Diagnosed <1 year ago							**HR 1.72 (1.50–1.96)**	
Cancer (non-haematological, versus none), Diagnosed 1–4.9 years ago							**HR 1.15 (1.05–1.27)**	
Cancer (non-haematological, versus none), Diagnosed ≥5 years ago							HR 0.96 (0.91–1.03)	
Blood cancer			HR 1.29 (0.97-1.71)	**HR 1.50 (1.06-2.12)**				
Blood cancer, Diagnosed <1 year ago							**HR 2.80 (2.08–3.78)**	
Blood cancer, Diagnosed ≥5 years ago							**HR 2.46 (2.06–2.95)**	
Blood cancer, Diagnosed 1–4.9 years ago							**HR 1.61 (1.39–1.87)**	
Respiratory tract cancer			HR 1.27 (0.89-1.81)	**HR 1.70 (1.16-2.49)**				
Radiotherapy in past 6 months			**HR 2.09 (1.48-2.96)**	**HR 2.11 (1.30-3.41)**				
Not on chemotherapy in past 12 months			reference	reference				
Chemotherapy grade A			**HR 1.74 (1.10-2.75)**	**HR 2.30 (1.35-3.94)**				
Chemotherapy grade B			**HR 3.50 (2.54-4.82)**	**HR 3.52 (2.29-5.42)**				
Chemotherapy grade C			**HR 3.37 (1.17-9.64)**	**HR 17.31 (6.5-46.0)**				
BMI								
18.5-24.9 (Normal weight)							reference	
≥ 30 (Obesity)		**HR 0.90 (0.83 to 0.99)**			**OR 1.62 (1.52, 1.74)**			
30 -34.9 (Obese class I)						OR 1.0 (0.7-1.4)[1], defined as overweight	HR: 1.05 (1.00–1.11)	
35–39.9 (Obese class II)							**HR: 1.40 (1.30–1.52)**	
≥40 (Obese class III)							**HR: 1.92 (1.72–2.13)**	
Smoking/ Substance abuse								
Never smoked							reference	
Current smoker							**HR: 0.89 (0.82–0.97)**	
Former smoker							**HR: 1.19 (1.14–1.24)**	
Substance abuse						OR 1.3 (0.7-2.2)[1]		
Alcohol abuse	**HR 1.12 (1.02–1.24)**					OR 1.3 (0.9-2.0)[1]		
Explanatory information	Data are the results of a multivariable logistic regression, which included the explanatory variables shown, plus region	Adjusted for all variables in the above column	Comorbidity models were adjusted for age and sex, age models were adjusted for sex, Charlson score and the ten specific chronic conditions 1 Charlson Comorbidity Index score, not number of comorbidities	Age, BMI, deprivation score, residency, ethnicity, kidney disease, cancer, diabetes, lung disease, heart disease, neurologic disease, mental illness, and more . All models were stratified by sex.	Age, sex, and smoking status, HBP, diabetes, obesity, asthma, immunosup., other CVDs, COPD, and CKD, multimorbidity	1=Included all variables medications and comorbidities and variables with p < 0.05 in the Univar. Log. regression analyses. 2= Incl. one med. at a time with all variables regarding comorbidities and vice versa + significant variables in the univariable analyses.	[1] = Age-, sex- and number of comorbidities adjusted OR (95% CI); tbl 4 in suppl. of original study; [2] = Age and sex-adjusted OR (95% CI)	Models were adjusted for age using a four-knot cubic spline for age, except for estimation of age-group hazard ratios.

Discussion and conclusion

We included ten studies assessing possible risk factors for hospitalisation, ICU admission/severe or critical illness, and COVID-19-related death. This is an addition of 5 new studies from our 3rd update of this report (October 15th, 2020). All included studies were however conducted during the first part of the pandemic, and possible changes in risk factors during later part are not captured. We excluded studies with fewer than 5000 laboratory test positive cases, and studies that only reported results from unadjusted univariate or bivariate analyses.

In this review update, older and increasing age continues to stand out as the predominant individual risk factor for hospital admission, severe disease, and COVID-19-related death. Male sex, race/ethnicity, deprivation score and obesity are all factors that also appear to be associated with increased risk. Furthermore, most comorbidities appear to be associated with increased risk, with increased number and severity of comorbid condition(s) appearing to be of compelling importance for increased risk of hospital admission, severity of disease and death.

This update provides more information on previously less well captured patient and population groups; More studies included individuals under 18 years of age, but results continue to be limited in representativeness as the total number of registered incidents for this age group remain small. Our findings correspond with a US study of 27,045 COVID-19 positive children, reporting that comorbidities were associated with hospitalisation and death, and that being below 10 years was associated with hospitalisation, compared to 10-18 years olds (15). Cohort studies reporting on risk factors in relation to more specific vulnerable subgroups in the population, like patients with mental illness, remain more limited. This reflects partially the prevalence of specific mental illnesses within societies but may also reflect data collection patterns. Findings in this report show that persons with severe mental illness (including schizophrenia, but broadly grouped) appear to have a heightened risk for hospital admission and death (6, 8). Yet no additional studies included in this update shed more light on this group, revealing that a population-based perspective may not capture the breadth of ongoing research. Two larger cohort studies (16, 17) providing more granular data on severe mental illnesses and schizophrenia separately have been published since our last literature search, however their methodology and narrow focus did not meet our inclusion criteria. Nevertheless, their findings strengthen our indication that severe mental illness, particularly schizophrenia, carry a higher risk for our reported outcomes. A study by Bitan et al. reported that schizophrenia patients had an increased risk for hospitalisation (OR 1.88 (95% CI 1.39–2.55)) and death (OR 3.27 (95% CI 1.39–7.68)), compared to non-schizophrenic controls (16). The second study by Yang et al. found slightly lower odds than Bitan for our reported outcomes, looking at a composition of several psychiatric disorders combined.

Some patient groups stand out as having particularly high risk for the studied outcomes, and further investigations are required to obtain more robust data for these population groups, for example for individuals with Down syndrome. Hence, although some information on risk for vulnerable groups is slowly emerging in population-based studies, further research is needed to strengthen the evidence on risk in certain vulnerable subgroups in the population. This is especially relevant for persons with rare conditions not well captured in population-based studies.

Generally, there is high agreement among study findings in relation to important risk factors, and this remains unchanged with the studies added in this update. For differing results there is a continuing need to identify and evaluate what the driving factors for these differences are. For example, there remains uncertainty on smoking as an independent risk factor. Smoking increases the risk of cardiovascular disease, cancer and chronic lung disease, all of which are risk factors for severe COVID-19. In analyses where one adjusts for both smoking and diseases caused by smoking, conflicting findings have been reported on smoking as a separate risk factor (7, 9). Therefore, further studies are needed to clarify the role of smoking as an independent risk factor in relation to COVID-19 related outcomes.

The outcome hospitalisation might also not be completely comparative or representative, as ease of, and criteria of access to care might vary from one setting to another. All included studies cover only the early period (until September 2020) of the pandemic, which may be less representative for the current situation with more exhaustive testing, better healthcare capacity and more effective treatment options available. Several other factors influence seeking medical care and hospital admission, e.g., higher out of pocket payments might disincentivise individuals seeking help, leading to only registration of more severe cases. This is particularly relevant to consider for studies from the USA, or other countries without universal healthcare. On the other hand, ease of access might overrepresent less severe cases, as suspected in the Danish study. In addition, organisational aspects of how care is provided vary between countries. In Norway, the national health authorities recommend nursing home patients with COVID-19 not to be admitted to hospital but managed within the nursing home setting.

Documentation for ICU admissions is less exhaustively covered compared to the other outcomes. The criteria for ICU admission might also be less clearly defined than for hospital admission or death. Moreover, ICU admission might not provide an accurate image of those with the most severe disease, but rather a combination of those with severe disease that have a better prognosis. Depending on available resources and a necessity for care triage, patients might be admitted to intensive care differently at different times. This is important to consider when interpreting the reported findings. Hence, ICU admissions might not provide a good basis for decisions relating to which population groups are at most risk for severe COVID-19 outcomes.

Nonetheless, since our last update the evidence base regarding important risk factors for hospital admission or death is more robust. We were able to reaffirm some of our previous findings and to expand and strengthen our evidence base. We were able to maintain the threshold for 5000 participants, while only looking at peer reviewed publications. Inadvertently the threshold choice might have led to some populations groups not being captured equally well, as seen in the absence of data on some vulnerable populations. Additionally, we performed quality assessment of included studies. We did not grade the certainty of evidence, which is why

the results from this review should still be interpreted with caution. It should be noted that only associations are reported in the included studies, hence causal relationships cannot be confirmed or refuted.

The included studies were heterogeneous in terms of statistical methods and procedures applied for selection of factors to include in the multivariate models. Some studies provided odds ratios and relative risks whereas other studies reported hazard ratios. As several registry studies looking at a similar population in the same country were included, there is a possibility that some study participants are included in more than one study. There was also large variability in the number of factors included in the multivariate models. One study reported all results separately for each sex (6). We also found large variability in the way different factors were categorised. Differences in reporting also represent differences in target population and characteristics, as for example ethnical groups in one location may not be representative for that of another location. Although patients were mostly representative for the general population, some studies analysed relevant variables only among COVID-19 tested or positive patients. The existing heterogeneity impairs direct comparison of risk estimates across studies, and meta-analysis was therefore not feasible.

While a certain amount of genetic variation was expected to occur as SARS-CoV-2 spreads, genomic surveillance has shown that variants with key mutations have outcompeted earlier variants, with dominant variants fluctuating by geographic region. This change in genetic landscape is not addressed in our included studies, and it cannot be excluded that newer variants may change the relevance of some risk factors. For example, early studies of the British variant indicate that there is an increased risk of death (18), although age continues to appear as the driving factor for severity (19). In how far other risk factors are affected remains uncertain. Genomic virus variation should be accounted for in future cohort studies, to better understand possible dynamics in risk factors.

Conclusion

In this 4th revision, previous findings are strengthened and expanded. The elderly are clearly the main group at risk of hospital admission, severe disease, and death if infected by COVID-19. Most comorbidities appear to increase risk, with increasing number and severity of comorbidities contributing to a further increase in the overall risk. Male sex, non-white ethnicity and deprivation are also associated with increased risk.

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Appendix

Appendix 1; Search strategy

Search: 2020-03-31

Ovid MEDLINE(R) ALL 1946 to March 31, 2021

1	(((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sars-coronavirus2 or sars-coronavirus-2 or sars-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemic*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.	
2	Hospitalization/ or exp Mortality/ or Critical Care/ or exp Intensive Care Units/ or exp Respiration, Artificial/ or (hospitalization* or hospitalization* or hospitalized or hospitalised or ((admit* or admission*) adj3 hospital*) or death* or mortality or ICU or ((intensive or critical) adj3 care) or ventilat* or intubat*).mp.	
3	Cohort Studies/ or Prospective Studies/ or Meta-Analysis.pt. or Systematic Review.pt. or (population-based or (large adj population*) or nationwide or nation-wide).mp. or (cohort* or systematic review or meta-analys*).ti.	
4	1 and 2 and 3	
5	(202010* or 202011* or 202012* or 202101* or 202102* or 202103*).dt.	
6	4 and 5	2226

Embase 1974 to 2021 March 31

1	(((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sars-coronavirus2 or sars-coronavirus-2 or sars-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemic*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.	
2	Hospitalization/ or exp Mortality/ or Intensive Care/ or exp Intensive Care Unit/ or exp Artificial Ventilation/ or (hospitalization* or hospitalization* or hospitalized or hospitalised or ((admit* or admission*) adj3 hospital*) or death* or mortality or ICU or ((intensive or critical) adj3 care) or ventilat* or intubat*).mp.	
3	Cohort Analysis/ or Prospective Study/ or Systematic Review/ OR Meta Analysis/ or (population-based or (large adj population*) or nationwide or nation-wide).mp. or (cohort* or systematic review or meta-analys*).ti.	
4	1 and 2 and 3	
5	Limit 4 to embase status	
6	(202010* or 202011* or 202012* or 202101* or 202102* or 202103*).dc.	
7	5 and 6	2597

Appendix 2; Excluded studies

Table of excluded studies

First author	Reason for exclusion
Batty (20)	Population size
Bitan (16)	Sample selection
Cho (21)	Population overlap
Drefahl (22)	Population overlap
Elliott (23)	Population size
Gu (24)	Population size
Hamer (25)	Sample selection
Lassale (26)	Population size
Lundon (27)	Sample selection
Moreira (15)	Population size
Maripuu (28)	Sample selection
Sallis (29)	Sample selection
Schonefeld (30)	Study design
Souza (31)	Sample selection
Yang (17)	Sample selection
Wahaibi (32)	Reporting detail
Wu (33)	Sample selection

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