BMJ Open Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: a systematic review and meta-analysis of observational studies

Yahya Mahamat-Saleh,1 Thibault Fiolet,1 Mathieu Edouard Rebeaud,2 Matthieu Mulot,3 Anthony Guihur,2 Douaee El Fatouhi,1 Nasser Laouali,1 Nathan Peiffer-Smadja,4,5,6 Dagfinn Aune,7,8,9,10 Gianluca Severi1,11

ABSTRACT

Objectives We conducted a systematic literature review and meta-analysis of observational studies to investigate the association between diabetes, hypertension, body mass index (BMI) or smoking with the risk of death in patients with COVID-19 and to estimate the proportion of deaths attributable to these conditions.

Methods Relevant observational studies were identified by searches in the PubMed, Cochrane library and Embase databases through 14 November 2020. Random-effects models were used to estimate summary relative risks (SRRs) and 95% CIs. Certainty of evidence was assessed using the Cochrane methods and the Grading of Recommendations, Assessment, Development and Evaluations framework.

Results A total of 186 studies representing 210 447 deaths among 1 304 587 patients with COVID-19 were included in this analysis. The SRR for death in patients with COVID-19 was 1.54 (95% CI 1.44 to 1.64, I²=92%, n=145, low certainty) for diabetes and 1.42 (95% CI 1.30 to 1.54, I²=90%, n=127, low certainty) for hypertension compared with patients without each of these comorbidities.

Regarding obesity, the SSR was 1.45 (95% CI 1.31 to 1.61, I²=91%, n=54, high certainty) for patients with BMI ≥30 kg/m² compared with those with BMI <30 kg/m² and 1.12 (95% CI 1.07 to 1.17, I²=68%, n=25) per 5 kg/m² increase in BMI. There was evidence of a J-shaped non-linear dose–response relationship between BMI and mortality from COVID-19, with the nadir of the curve at a BMI of around 22–24, and a 1.5–2-fold increase in COVID-19 mortality with extreme obesity (BMI of 40–45). The SRR was 1.28 (95% CI 1.17 to 1.40, I²=74%, n=28, low certainty) for ever, 1.29 (95% CI 1.03 to 1.62, I²=84%, n=19) for current and 1.25 (95% CI 1.11 to 1.42, I²=75%, n=14) for former smokers compared with never smokers.

The absolute risk of COVID-19 death was increased by 14%, 11%, 12% and 7% for diabetes, hypertension, obesity and smoking, respectively. The proportion of deaths attributable to diabetes, hypertension, obesity and smoking was 8%, 7%, 11% and 2%, respectively.

Conclusion Our findings suggest that diabetes, hypertension, obesity and smoking were associated with higher COVID-19 mortality, contributing to nearly 30% of COVID-19 deaths.

Trial registration number CRD42020218115.

INTRODUCTION

COVID-19 is a viral infectious disease caused by SARS-CoV-2, which was first reported in Wuhan City, China, in December 2019.1 SARS-CoV-2 has since spread to all countries worldwide and COVID-19 has been declared a pandemic by the WHO.2 As of 24 August 2021, over 212.3 million cases and 4.4 million deaths have been reported globally since the start of the pandemic.3 Age is the main risk factor for poor outcome in people with COVID-19 infection,4,5 as it is correlated with more comorbidities. About 70%–87% of COVID-19 deaths are among people aged 70 years or older.6,7 Patients with comorbidities, including diabetes, cardiovascular disease, respiratory disease, chronic kidney disease and others chronic diseases are at increased risk of developing severe or critical COVID-19,8,9 which may partly explain a greater mortality in hospital.10-14 Studies suggest that
about 20%–51% of patients hospitalised with COVID-19 have at least one comorbidity.10 15

Previous meta-analyses reported a higher mortality rate from COVID-19 in patients with comorbidities.16–22 Ssen-tongo et al, based on 25 studies published from December 2019 to 9 July 2020, suggested that diabetes and hypertension were respectively associated with a 1.48-fold and 1.82-fold greater risk of COVID-19 death compared with those without these comorbidities.16 Based on studies published during the same period, Luo et al reported similar results.17 Du et al found that patients with obesity had a 2.68-fold risk of dying from COVID-19 compared with non-obese patients.18 Most of the published meta-analyses did not investigate the shape of the dose–response relationship between body mass index (BMI) and risk of death in order to clarify whether the association is dose-dependent or if there are threshold effects.20 23–25 In addition, evidence suggests that smoking may increase risk of severe disease and death from COVID-19.19 However, it is not clear whether such an increase in COVID-19 mortality is different in current and past smokers since previous meta-analyses have not performed separate analyses.19 26 27

However, since the publication of these meta-analyses, several observational studies have been published on diabetes, hypertension, obesity or smoking and risk of death in patients with COVID-1919 28–122 and the strength of the associations differed greatly between studies. Moreover, the proportion of deaths attributable to diabetes, hypertension, obesity or smoking habits has not been estimated. This last aspect may help adapting public health measures and vaccination strategies to populations at risk of severe COVID-19.

Given the rapidly increasing death from COVID-19 globally, and since diabetes, hypertension, obesity and tobacco smoking represent the most important public health problems worldwide, which contributed to higher risk of death globally; we thus conducted a systematic review and meta-analysis of published observational studies to investigate the association between diabetes, hypertension, smoking and obesity and risk of death in patient with COVID-19 and to clarify the strength of these associations. We further estimated the proportion of deaths attributable to these conditions.

In addition, we searched the reference lists of the relevant publications, reviews and meta-analyses to identify additional potentially relevant studies. We only included observational studies (cohort studies and cross-sectional) that reported relative risk estimates (such as hazard ratios (HRs), relative risk (RR) or odds ratios (ORs)) with the 95% CIs with or without adjustment for potential confounders. The search was independently screened by two researchers (YM-S and TF) and discrepancies were resolved by discussion with a third researcher (MER).

Data collection
From each included publication, we extracted results and study characteristics which included first author’s last name, publication year, country where the research was conducted in, study design, study description or name, study period, sample size with number of deaths, exposure, categories, risk estimate and 95% CIs, and adjustment factors. Data were extracted by YM-S and extractions were checked for accuracy by TF. Discrepancies were resolved through discussion with a third researcher (MER).

Quality assessment and risk of bias
The quality of individual studies was assessed independently by two researchers (YM-S and TF) using the Cochrane risk of bias tool ROBINS-I, which grades studies on a scale from critical risk of bias to low risk of bias considering bias due to confounding, selection of study participants, exposure measurement, misclassification of exposure during follow-up, missing data, measurement of outcomes and bias due to selection of reported results.124 Following the assessment of risk of bias, the body of evidence for each comorbidity and risk of death was rated independently using the Grading of Recommendations, Assessment, Development and Evaluations approach.125 Discrepancies were resolved through discussion with a third researcher (DA).

Data analysis
We used random effects models that consider both within study and between-study variation to calculate summary RR (SRRs) (95% CIs) of COVID-19 mortality for patients with diabetes compared with those without diabetes, for patients with hypertension versus those without hypertension, for obese versus non-obese and for current, former and ever smoker compared with never smokers. The natural logarithm of the RR was weighted using random effects weights.127 Statistical heterogeneity between studies was assessed by the Cochrane Q test and the I² statistic.128 We calculated the absolute risk difference (RD) from the baseline risk of mortality (BR) from Docherty et al19 large cohort and relative risk (RR) using the formula RD=BR×(RR−1).130

We further performed a dose–response analysis for the associations between BMI and COVID-19 mortality using the method described by Greenland and Longnecker to compute the linear trend from the natural logs of the RR and CIs across categories of BMI.131 We calculated SRRs

MATERIALS AND METHODS

Search strategy and selection criteria
The meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement125 and Meta-Analysis of Observational Studies in Epidemiology.124 This study was registered and accepted in the International Prospective Register of PROSPERO in October 2020. PubMed (MEDLINE), Cochrane library and Embase databases were searched to identify relevant articles published in English from December 2019 to 14 November 2020. The search terms that we used are provided in online supplemental file.
and 95% CIs for a 5-unit increment in BMI using random effects models. This method required mean or median of BMI, RRs and 95% CIs for at least three categories. The mean or median BMI level per category was used if provided in the publication, and if not, the midpoint of the upper and lower boundaries was estimated as a range in each category. When the highest and lowest categories were open-ended, we used the width of the adjacent interval to estimate the upper and lower boundaries for the category. For studies that reported results separately for young and adults, for current and former smoker, but not overall, we pooled the results using a fixed-effects model as reported by the Hamling procedure to obtain an overall estimate to be used in the meta-analysis.132

To explore the potential non-linear dose–response relation between BMI and mortality among patients with COVID-19, we used fractional polynomial models.133 We determined the best fitting second order fractional polynomial regression model, defined as the one with the lowest deviance. Only studies which presented more than two categories of BMI were included in the non-linear analysis. Subgroup and meta-regression analyses were conducted to investigate potential sources of heterogeneity. Small-study effects, such as publication bias, were visually assessed by examining funnel plots for asymmetry, and with Egger’s test,134 and the results were considered to indicate potential small-study bias when p values were <0.10. We conducted sensitivity analyses excluding one study at a time to clarify whether the results were driven by one large study or a study with an extreme result.

We finally calculated the population attributable fraction (PAF) of mortality among patients with COVID-19 due to diabetes, hypertension, obesity and smoking, worldwide using the following formula135.

$$\text{PAF} = \frac{p \times (RR - 1)}{[p \times (RR - 1)] + 1}$$

Where RR was the relative risk, p was the prevalence of the exposure in patient with COVID-19. The prevalence of diabetes (11.5%), hypertension (22.9%), obesity (29%) and smoking (9%) were obtained from previous meta-analyses.136–138

**Patient and public involvement**

Patients or the public were not involved in any aspect of the study design, conduct or in the development of the research question or outcome measures.

**RESULTS**

A total of 6007 records were identified in MEDLINE, Cochrane library and in EMBASE (figure 1). A total of 4665 publications were excluded after reading title and abstract or because of duplicates. Among 1342 full-text articles retrieved, 994 were excluded as not meeting the inclusion criteria, leaving a total of 348 publications. Of these, 162 articles were not eligible because they lacked sufficient data,139 140 reported no risk estimate or irrelevant data,139 140 because they had identical populations141–151 or were retracted.152 Finally, a total of 186 observational studies were included in this meta-analysis. Of the included studies, 58 were from Europe, 58 from North America, 60 from Asia, 6 from South America and 4 from Africa (online supplemental table 1). From the 186 publications assessed using the ROBINS-I tool, 92 were evaluated as being at low risk of bias, 49 at moderate risk of bias and 46 at high risk of bias because of insufficient adjustment of relevant confounders (online supplemental table 2).

**Diabetes and mortality in patient with COVID-19**

A total of 145 studies4 28–119 121 122 129 153–201 were included in the analysis of the association between diabetes and mortality, including a total of 198 491 deaths among 1 165 897 patients with COVID-19. The SRR for diabetes patients compared with those without diabetes was 1.54 (95% CI 1.44 to 1.64) and there was high heterogeneity among studies (I²=92%). We found that diabetes increased the absolute risk of death by 14% (table 1). The funnel plot did not provide evidence of publication bias (online supplemental figure 1) and we found no evidence of small study effects (Egger’s test, p value=0.54).

The positive association persisted across all subgroups analyses stratified by study design, number of patients, geographic location and adjustment for some confounding factors (table 2). However, meta-regression analyses suggested some indication of heterogeneity between studies that adjusted for multiple factors such as age, sex and other comorbidities versus studies without such adjustment or adjusted for age only (P heterogeneity=0.003), with a stronger association for the studies with no adjustment factors or those adjusted for age only. The
positive association was also stronger among studies with critical or serious risk of bias compared with those with moderate or low risk of bias, with heterogeneity detected across studies (Pheterogeneity=0.001). The influence analysis showed no substantial influence of any of the included studies on the global estimate of diabetes and mortality. The SRR ranged from 1.51 (95% CI 1.42 to 1.61) when excluding the Barbu et al study\textsuperscript{35} to 1.55 (95% CI 1.45 to 1.64) when excluding the Meng et al study\textsuperscript{114} (online supplemental figure 2).

We included 127 observational studies\textsuperscript{4} 29 30 32 33 35–40 42–45 47–50 52–56 58 59 61–63 65 66 69 71–76 78 81–84 86 88–90 92–95 97 103 105 106 108–112 114–118 120–122 153 154 156–159 161–167 169 173–180 182–188 193–200 202–219 in the analysis of the association between hypertension and mortality, including a total of 113,243 deaths among 934,958 patients with COVID-19. The SRR for hypertension patients versus those without hypertension was 1.42 (95% CI 1.30 to 1.54) with high evidence of heterogeneity (I²=90%) (table\textsuperscript{1}). The absolute risk of death for patients with COVID-19 with hypertension compared with without hypertension was increased by 11%. Small study effects, such as publication bias, were not indicated with the funnel plot (online supplemental figure 3) or Egger's test (p value=0.26). Here again, the positive association persisted in most subgroup analyses (table\textsuperscript{2}). Our meta-regression analysis showed that study design and the geographic location did not significantly alter the overall estimate (online supplemental table 3). When excluding the most influential studies one by one, the positive association was also stronger among studies with critical or low risk of bias, with heterogeneity detected across studies (Pheterogeneity≤0.0001).

We investigated BMI and mortality risk including 145,605 deaths among 808,574 patients with COVID-19. \textsuperscript{29} 32 38 44 45 48 49 52 61 62 64 65 67 69 73 74 79 84–86 88–90 93 99 103 107 118 120–122 129 154 164 165 178 181 182 184 192 196 197 202 206 220–228 investigated BMI and mortality risk including 145,605 deaths among 808,574 patients with COVID-19. The analysis yielded an SRR of 1.45 (95% CI 1.31 to 1.61) for obese (BMI ≥30 kg/m\textsuperscript{2}) versus non-obese (BMI <30 kg/m\textsuperscript{2}) patients, with high heterogeneity detected between studies (I²=91%) (figure 2) (table\textsuperscript{1}). We found that obesity increased the absolute risk of death by 12%. There was no statistically significant evidence of publication bias (P value Egger’s test=0.29). Here again, the positive association persisted in most subgroup analyses (figure 2). Our meta-regression analysis showed that study design and the geographic location did not significantly influence the overall association. However, heterogeneity between subgroup analyses was observed. Therefore, we performed meta-regression analyses stratified by age only or for multiple factors (P values Egger’s test=0.39 and 0.73, respectively). Figure 3 of Egger’s test 𝑀📊(values) shows that the study design and the geographic location did not significantly influence the overall association. However, heterogeneity between subgroup analyses was observed. Therefore, we performed meta-regression analyses stratified by age only or for multiple factors (P values Egger’s test=0.39 and 0.73, respectively). When excluding the most influential studies, we found no substantial influence of any of the included studies (online supplemental figure 4).

| Prognostic factors | Number of studies | SRR (95% CI) | I² (%) | Risk difference (95% CI) (%) | PAF (95% CI) (all included studies) (%) | PAF (95% CI) (fully adjusted studies) (%) | Number of patients | Number of deaths |
|--------------------|------------------|-------------|--------|-----------------------------|------------------------------------------|--------------------------------------------|------------------|------------------|
| Diabetes           | 145              | 1.54 (1.44 to 1.64) | 92     | +14 (+11 to +17) | 10.6 (8.8 to 12.4) | 8.1 (6.2 to 9.7) | 1 165 897     | 198 491         |
| Hypertension       | 127              | 1.42 (1.30 to 1.54) | 90     | +11 (+8 to +14)  | 11.8 (8.7 to 14.7) | 6.9 (4.0 to 9.6) | 934 958       | 113 243         |
| Obesity            | 54               | 1.45 (1.31 to 1.61) | 91     | +12 (+8 to +16)  | 11.5 (8.2 to 15.0) | 11.1 (7.1 to 15.0) | 858 374       | 145 605         |
| Ever smoking       | 28               | 1.28 (1.17 to 1.40) | 74     | +7 (+4 to +10)   | 2.45 (1.5 to 3.5) | 2.0 (0.8 to 3.3) | 47 096        | 11 333          |

I² (%) is a measure of the proportion of the heterogeneity attributed to between study variation rather than due to chance. I² values of 25%, 50% and 75% indicates low, moderate and high between study heterogeneity, respectively.

CI, confidence interval; PAF, population attributable fraction of mortality; SRR, summary relative risk.
the global estimate did not substantially change (online supplemental figure 6).

Twenty-five studies (32 072 deaths among 95 852 patients with COVID-19)38 56 61 74 86 89 91–93 97 108 111 112 161 162 175 177 221 222 229–235 were included in the dose–response meta-analysis of BMI and mortality risk. The summary RR for a 5 kg/m² increment in BMI was 1.12 (95% CI 1.07 to 1.17, I²=68%) (figure 3) and no statistically significant evidence of publication bias (p value=0.11) or by inspection of the funnel plot was observed (online supplemental figure 7). However, evidence of a J-shaped non-linear relation between BMI and mortality risk was observed (P non-linearity ≤0.0001), suggesting a flat dose–response curve at a BMI around 22–24 kg/m² with a slight increase in risk of death below that range and a 1.5–2-fold increase in risk of death with a BMI of 40–45 versus 22–24 kg/m² (figure 4).

In sensitivity analyses excluding one study at a time from the analysis, the summary for a 5 kg/m² increment in BMI ranged from 1.11 (95% CI 1.06 to 1.15) when excluding the Czernichow et al. Study108 to 1.13 (95% CI 1.08 to 1.19) when excluding the Ferrando-Vivas et al study230 (online supplemental figure 8).

### Smoking and mortality in patient with COVID-19

Twenty-eight studies38 40 56 61 63 66 67 76 93 97 103 108 110 111 118 121 129 161 164–166 175 177 183 232 236–238 were included in the analysis of ever smoking versus never smoking and mortality with a total of 11 333 deaths among 47 096 patients with COVID-19. The SRR for hospital death in patient with COVID-19 was 1.28 (95% CI 1.17 to 1.40, I²=74%) for ever smokers versus never smokers (figure 5). The absolute risk of death for smoking was increased by 7% (table 1).

| Table 2 Subgroup analyses of association between diabetes and hypertension and mortality risk in patients with COVID-19 |
|---|---|---|---|---|---|---|---|---|
| Diabetes | | | Hypertension | | | | | |
| | n | SRR (95% CI) | I² (%) | P within * | P between † | n | SRR (95% CI) | I² (%) | P within * | P between † |
| All studies | 145 | 1.54 (1.44 to 1.64) | 91.7 | <0.0001 | | 127 | 1.42 (1.30 to 1.54) | 90.1 | <0.0001 |
| Study design | | | | | | | | | | |
| Retrospective | 129 | 1.54 (1.44 to 1.64) | 91.7 | <0.0001 | | 112 | 1.42 (1.30 to 1.56) | 90.9 | <0.0001 |
| Prospective | 11 | 1.28 (1.12 to 1.48) | 70.0 | <0.0001 | | 9 | 1.21 (0.98 to 1.50) | 73.4 | <0.0001 |
| Cross-sectional | 5 | 2.47 (1.56 to 3.94) | 81.4 | <0.0001 | 0.05 | 6 | 1.70 (1.18 to 2.44) | 61.8 | 0.02 | 0.50 |
| Geographical location | | | | | | | | | | |
| North America | 45 | 1.33 (1.19 to 1.48) | 90.3 | <0.0001 | | 40 | 1.30 (1.12 to 1.50) | 93.4 | <0.0001 |
| South America | 6 | 1.54 (1.27 to 1.87) | 93.7 | <0.0001 | | 2 | 2.03 (0.99 to 4.18) | 69.1 | 0.072 |
| Europe | 46 | 1.53 (1.36 to 1.72) | 93.8 | <0.0001 | | 43 | 1.36 (1.20 to 1.54) | 82.8 | <0.0001 |
| Asia | 43 | 1.94 (1.65 to 2.29) | 75.1 | <0.0001 | | 38 | 1.62 (1.28 to 2.04) | 86.1 | <0.0001 |
| Africa | 5 | 1.56 (0.92 to 2.62) | 87.3 | <0.0001 | 0.10 | 4 | 1.08 (0.86 to 1.35) | 14.9 | 0.318 | 0.33 |
| Number of patients | | | | | | | | | | |
| <1000 | 79 | 1.73 (1.52 to 1.97) | 74.8 | <0.0001 | 0.001 | 78 | 1.56 (1.36 to 1.79) | 74.8 | <0.0001 |
| ≥1000 | 66 | 1.43 (1.32 to 1.55) | 95.4 | <0.0001 | | 49 | 1.28 (1.14 to 1.44) | 94.8 | <0.0001 | <0.0001 |
| Patients admission unit | | | | | | | | | | |
| Non-ICU admitted | 142 | 1.55 (1.45 to 1.66) | 91.6 | <0.0001 | 0.24 | 125 | 1.43 (1.31 to 1.56) | 90.2 | <0.0001 | 0.28 |
| ICU admitted | 3 | 1.22 (1.14 to 1.30) | 0.0 | 0.81 | | 2 | 0.98 (0.82 to 1.17) | 0.0 | 0.81 |
| Risk of bias | | | | | | | | | | |
| Low | 72 | 1.46 (1.34 to 1.59) | 92.4 | <0.0001 | | 63 | 1.17 (1.08 to 1.29) | 80.2 | <0.0001 |
| Moderate | 37 | 1.28 (1.19 to 1.39) | 64.9 | <0.0001 | | 34 | 1.34 (1.13 to 1.59) | 88.9 | <0.0001 |
| Serious | 17 | 1.90 (1.44 to 2.51) | 86.4 | <0.0001 | | 15 | 1.83 (1.42 to 2.37) | 84.4 | <0.0001 |
| Critical | 19 | 2.11 (1.61 to 2.77) | 93.4 | <0.0001 | 0.001 | 15 | 2.64 (1.61 to 4.34) | 96.3 | <0.0001 | <0.0001 |
| Adjustment for confounders | | | | | | | | | | |
| No | 21 | 2.09 (1.62 to 2.69) | 89.4 | <0.0001 | | 17 | 2.54 (1.62 to 3.99) | 95.9 | <0.0001 |
| Age only | 18 | 1.90 (1.56 to 2.31) | 85.4 | <0.0001 | 0.003 | 14 | 1.78 (1.36 to 2.32) | 85.1 | <0.0001 |
| Multiple | 106 | 1.40 (1.30 to 1.49) | 87.5 | <0.0001 | | 96 | 1.23 (1.13 to 1.33) | 85.4 | <0.0001 | <0.0001 |

I² (%) is a measure of the proportion of the heterogeneity attributed to between study variation rather than due to chance. I² values of 25%, 50% and 75% indicates low, moderate and high between study heterogeneity, respectively.

*P value for heterogeneity within each subgroup.
†P value for heterogeneity between subgroups with meta-regression analysis.
CI, confidence interval; ICU, intensive care unit; SRR, summary relative risk.
In sensitivity analyses, the results persisted when excluding one study at a time (online supplemental figure 10).

For current smoking versus never smoking, nineteen studies, which included 9845 deaths among 33,147 patients with COVID-19, were identified. The SRR of current smoking was 1.29 (95% CI 1.03 to 1.62, I²=84%) (figure 6) and no statistically significant evidence of publication bias was observed (p value=0.86) (online supplemental figure 11).

A total of 14 studies were included in the analysis of former smoking versus never smoking and mortality risk, including 8121 deaths among 25,340 patients with COVID-19. The SRR was 1.25 (95% CI 1.11 to 1.42) with moderate to high heterogeneity (I²=75%) (figure 7). There was no evidence of publication bias with Egger’s test (p value=0.70). In sensitivity analyses excluding one study at a time from the analyses of current and former smoking, the results were not materially altered (online supplemental figures 12-13).

Globally, results did not change in nearly all subgroup analyses (online supplemental table 4).

Finally, a total of 15 studies did not provide a definition of the smoking variable (>76400 deaths, 682310 patients) and the SRR was 1.31 (95% CI 1.07 to 1.62, I²=88%) (online supplemental figure 14) which seemed to be similar to current and ever smoking.

Figure 2 Association between obesity and mortality risk in patients with COVID-19.

(p value=0.91) (online supplemental figure 9). In sensitivity analyses, the results persisted when excluding one study at a time (online supplemental figure 10).

PAF of deaths and assessment of certainty of the body of evidence

The estimated PAF was 10.6%, 11.8%, 11.5% and 2.5% for diabetes, hypertension, obesity and ever smoking, respectively when considering all studies included in this meta-analysis (table 1). Based on studies that adjusted for multiple risk factors, attributable death was 8% for
patients with diabetes had a 54% higher risk of death from COVID-19 compared with patients without diabetes; those with hypertension had a 42% increase in the relative risk of death from COVID-19 compared with patients without hypertension and those with obesity have a 45% greater in the relative risk of COVID-19 death compared with non-obese patients. In addition, we found that ever, current and former smoking was associated with 28%, 29% and 25% increases in the relative risk of death in patients with COVID-19.

Our linear dose–response meta-analysis suggested that each 5 kg/km² increment in BMI was associated with a 12% greater risk of COVID-19 death. However, evidence of non-linearity was observed in the analysis of BMI and risk of COVID-19 death, with a J-shaped dose–response relation with flattening of the dose–response curve between 22 and 24 of BMI level and a slight increase below that range and a 1.5–2-fold increase in risk with a BMI of 40–45. While there was no publication bias, study heterogeneity was high for all exposures and this persisted in most of the subgroup analyses. However, the heterogeneity appeared to be driven to a larger extent by differences in the strength of the associations, than differences in the direction of the effect, as the vast majority of studies reported significant or non-significant positive associations between these exposures and increased mortality, and relatively few studies reported risk estimates in the direction of an inverse association. Given this meta-analysis included more studies than a typical meta-analysis, I² and heterogeneity were high as the likelihood of divergent findings increases with increasing number of studies.

Comparisons to findings from previous epidemiological studies and biological mechanisms
Since the first reports of COVID-19, several studies have shown that patients with COVID-19 with comorbidities have a higher risk of death. However, these studies
have differed greatly in term of sample size, and results are conflicting and heterogeneous. Previous meta-analyses have shown that patients with diabetes, hypertension and obesity had an increased risk of mortality.\textsuperscript{16–18, 21, 24–27} Unfortunately, these previous meta-analyses were limited by the lack of subgroup analyses, which is crucial to evaluate heterogeneity and no previous meta-analysis has estimated the number of deaths attributed to these comorbidities or conditions.

This meta-analysis summarises the results of 186 observational studies published up to November 2020, including 210,447 deaths among 1,304,587 million patients with COVID-19. Our findings are similar to results from previously published systematic reviews, suggesting a higher mortality rate of COVID-19 in patients with cardiovascular or chronic condition.\textsuperscript{16–17, 21, 22} We found a 1.54-fold greater mortality from COVID-19 among patient with diabetes compared with those without (n=145 studies), which is similar to those yielded in previous meta-analyses,\textsuperscript{16} whereas the estimate magnitude is weaker than those in de Almeida-Pititto et al.\textsuperscript{21} Kumar et al.,\textsuperscript{246} Shang et al.\textsuperscript{247} and Luo et al.\textsuperscript{17} In our subgroup analyses, we found that the positive association was stronger in studies without any adjustment or adjusted for age only compared with studies that adjusted for multiple factors. Thus, the higher magnitude observed in the previous meta-analyses may be in part due to the important number of studies without adjustment for confounding factors such as age and comorbidities, which are mostly with critical or serious risk of bias. In addition, we estimated that 8% of deaths by COVID-19 were attributed to diabetes; this aspect has to our knowledge not been investigated previously. The absolute risk of death associated with diabetes was increased by 14%. The mechanism underlying the increased mortality from COVID-19 in patients with diabetes may be explained by chronic inflammatory conditions. Patients with COVID-19 with diabetes have a significantly higher inflammatory markers such as C reactive protein (CRP), interleukin 6 (IL-6) compared with patients without diabetes.\textsuperscript{249} Inflammatory markers such as IL-6, CRP, IL-10, lactate dehydrogenase and tumor necrosis factor-α, which are indicative of different aspects of COVID-19 severity, requirements of intensive care support including dialysis and ventilation, are associated with higher risk of death.\textsuperscript{250, 251}

Regarding hypertension, our findings yielded a 1.42-fold higher risk of death from COVID-19 in patient with hypertension (n=127 studies), which also is slightly weaker than the results from previous meta-analyses.\textsuperscript{16–22, 24–27} Nearly 7% of death in patients with COVID-19 could be attributed to hypertension and we found that hypertension increased the absolute risk of death by 11%. Previous clinical studies showed that hypertension is a major risk factor for worse outcome in patients infected with SARS and Middle East respiratory syndrome.\textsuperscript{252–253} Although, the exact mechanism by which hypertension increase mortality rate remains unclear, chronic inflammation may play an active role in increasing risk of death.

Du et al suggested that patients with obesity had a 2.68-fold risk for COVID-19 mortality compared with non-obese patients (n=7 studies).\textsuperscript{18} In dose–response analysis, they showed that for each 1 kg/m\textsuperscript{2} increase in BMI, the risk of death increased by 6%. Partly consistent with this study, we found that a 5 kg/m\textsuperscript{2} increase in BMI level was associated with a 12% increase in the risk of death in patient with COVID-19 (n=25 studies). In addition, we found evidence of a non-linear J-shaped association between BMI and mortality from COVID-19, with a flattening of the dose–response curve for BMI values between 22 and 24 kg/m\textsuperscript{2} and with a slightly higher risk below that range and a moderate to strong increase in mortality with severe obesity (BMI 40–45). Obesity is associated with a low-grade systemic inflammation, which plays a major role in the pathogenesis of respiratory conditions. Patients with COVID-19 and with preexisting obesity may have an overactivated inflammatory response, which may induce excessive inflammatory response.\textsuperscript{254} Obesity is also strongly associated with increased risk of diabetes, hypertension and several other chronic diseases\textsuperscript{255} that increases risk of COVID-19 mortality.\textsuperscript{256}

In addition, our finding showed that ever, current and former smoking was associated with 28%, 29% and 25% increases in the relative risk of death in patients with COVID-19 compared with never smokers. Tobacco smoking is known to alter the function of the immune system; therefore smokers are more likely to get a severe infection of COVID-19 due to their poor mucociliary clearance, which could lead to the release of pro-inflammatory markers and oxidative stress and thereby contribute to higher mortality rates. The risk of death in former smokers was higher than in never smokers and only slightly lower than risk in current smoker. However, more studies are required to clarify the impact of longer durations of smoking cessation in former smokers on risk of death in patients with COVID-19.

Although we found that diabetes, hypertension, BMI and smoking were associated with greater COVID-19 mortality, a recent meta-analysis suggested that mortality was more frequently observed in patients with COVID-19 with cardiovascular disease, cerebrovascular accident and chronic kidney disease.\textsuperscript{257} The authors observed that COVID-19 mortality among all comorbidities was high in European and Latin American patients compared with the US patients. It is possible that geographical differences in therapeutic practice of COVID-19 such as the use of antibiotics, antivirals and others drugs may partly explain the greater COVID-19 death in some regions,\textsuperscript{258} while there was no evidence of heterogeneity in findings across geographic location in our study. The review also suggested that COVID-19 mortality among those with underlying medical diseases was high in mostly elderly patients.\textsuperscript{258} However, we did not perform subgroup analysis by age because this information was lacking in most of the included studies.
Strengths, limitations and public health implications

This present meta-analysis of observational studies on diabetes, hypertension, obesity and smoking and risk of death in patients with COVID-19 has several strengths, including the large sample size and number of COVID-19 deaths, the detailed subgroup and sensitivity analyses, as well as the linear and non-linear dose–response analyses, which clarified the strength and shape of the dose–response relationship. Original aspects of our study included the estimation of the number of deaths attributable to these conditions. This is, to our knowledge, the first meta-analysis that perform a separate analysis of ever, current and former smoking versus never smoking in relation to COVID-19 mortality. As any previous published meta-analyses, the current analysis has some limitations that should be considered in the interpretation of our findings. First, we did not investigate the association between presence of two or more coexisting comorbidities and risk of death in patients with COVID-19. Finally, subgroup analyses stratified by clinical or lifestyle factors such as medications, diabetes type and duration, adherence to specific diet, or physical activity were not possible because of the lack of such data from the studies included.

Despite these limitations, our findings may have important public health implications in the context of increasing numbers of severe COVID-19 cases, overburdened hospitals and leading to higher hospital death due to COVID-19 and suggest that people with cardiovascular risk factors, in particular those with diabetes, hypertension and obesity, should be considered as a high priority to get vaccinated. In addition, since smoking is a risk factor for several chronic diseases, including cancer and cardiovascular disease, our finding lend support to the importance of smoking prevention and smoking cessation and support policies and public health efforts to reduce the prevalence smoking in the general population.

CONCLUSION

Our finding suggests that presence of diabetes, hypertension, obesity and smoking in patients with COVID-19 is associated with a 1.54-fold, 1.42-fold, 1.45-fold and 1.28-fold greater risk of mortality, respectively. We have found that the proportion of death attributable to diabetes, hypertension, obesity and smoking was 8%, 7%, 11% and 2%, respectively. These findings support that people with diabetes, hypertension, obesity should be prioritised for vaccination in order to limit the higher death rates in hospital. Public policies should promote a healthier lifestyle including healthier diets and regular physical activity to reduce patient risk factors and comorbidities.

REFERENCES

1 Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med Overseas Ed 2020;382:727–33.
2 WHO. Coronavirus disease (COVID-19) pandemic, 2020. Available: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAIA657D_BRAZeIwAzcfcxWrmZaIFQwmw6gYIEsv692KLm7Td5uQwaSN7-Hq0rjcu-rGFyBoCt1IQAvD_BwE
3 World Health Organization (WHO). Who coronavirus disease (COVID-19) Dashboard. Available: https://covid19.who.int/?gclid=CjwKCAIA657D_BRAZeIwAzcfcxWrmZaIFQwmw6gYIEsv692KLm7Td5uQwaSN7-Hq0rjcu-rGFyBoCt1IQAvD_BwE

Author affiliations
1 Paris-Saclay University, UVSQ, Inserm, Gustave Roussy, “Exposome and Heredity” team, CESP, F-94805, Villejuif, France
2 Department of Plant Molecular Biology, Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland
3 Laboratory of Soil Biodiversity, Faculty of Science, University of Neuchâtel, Neuchâtel, Switzerland
4 Université de Paris, IAME, INSERM, Paris, France
5 National Institute for Health Research, Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, Imperial College London, London, UK
6 Infectious and Tropical Diseases Department, Bichat-Claude Bernard Hospital, AP-HP, Paris, France
7 Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK
8 Department of Nutrition, Bjerkes University College, Oslo, Norway
9 Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway
10 Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
11 Department of Statistics, Computer Science and Applications “G. Parenti”, University of Florence, Florence, Italy

Twitter Yahya Mahamat-Saleh @MS_Y Thibault Fiolet @TF_Fiolet Mathieu Edouard Rebeaud @Damkyan Omega and Anthony Gulhr @AnthonyGulhr

Contributors YM-S conceived and designed the research. YM-S performed statistical analysis and wrote the first draft of the paper. YM-S, TF and MER performed the literature search and literature screening. YM-S and TF assessed the risk of bias of the studies and assessed the certainty of evidence of the associations. MM assisted with the statistical analysis. YM-S, TF, MER, MM, AG, DEF, NL, NP-S, DA and GS contributed to data interpretation and revision of the manuscript for intellectual content. YM-S takes responsibility for the integrity of the data and the accuracy of the data analysis. YM-S is responsible for the overall content as guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Yahya Mahamat-Saleh http://orcid.org/0000-0002-5892-8886
Anthony Gulhr http://orcid.org/0000-0001-5353-1428
Daglinn Aune http://orcid.org/0000-0002-4533-1722
Open access

4 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.

5 Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA 2020;323:1775–1776.

6 Goldstein JR, Lee RD. Demographic perspectives on the mortality of COVID-19 and other epidemics. Proc Natl Acad Sci USA 2020;117:22035–41.

7 Dembygenes Y, COVID-19 age-mortality curves are flatter in developing countries 2020.

8 Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020;323:2696–9.

9 Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061.

10 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395:497–506.

11 Yang J, Zheng Y, Guo X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020;94:91–5.

12 Siordia JA, Epidemiology and clinical features of COVID-19: a review of current literature. J Clin Virol 2020;127:104357.

13 Guan W-J, Liang W-H, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020;55:2000547.

14 Khan MMA, Muhajarine N, Mustagir MG, et al. Effects of underlying morbidity on the occurrences of deaths in COVID-19 patients: a systematic review and meta-analysis. J Glob Health 2020;10:020503.

15 Liu K, Fang Y-Y, Deng Y, et al. Clinical characteristics of novel coronavirus pneumonia cases in tertiary hospitals in Hubei Province, China. Chin Med J 2020;133:1025–31.

16 Ssentongo P, Ssentongo AE, Heilbrunn LS, et al. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. PLos One 2020;15:e0233147.

17 Luo L, Fu M, Li Y, et al. The potential association between common comorbidities and severity and mortality of coronavirus disease 2019: a pooled analysis. Clin Cardiol 2020;43:1478–93.

18 Du Y, Lv Y, Zha W, et al. Association of body mass index (BMI) with COVID-19 clinical outcomes. J Infect Chemother 2020;26:1657–9.

19 Hussain A, Mahawar K, Xia Z, et al. Obesity and mortality of COVID-19: meta-analysis. Obes Res Clin Pract 2020;14:295–300.

20 de Almeida-Outt A, Ballouze R, Ooi JP, et al. Associations of type 1 and 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol 2020;8:813–22.

21 Bocca MG, Thompson RJ, Thompson DC, et al. The impact of SARS-CoV-2 on the most common Comorbidities—A retrospective study on 814 COVID-19 deaths in Romania. Front Med 2020;7:567199.

22 Boule A, Davies M-A, Hussey J, et al. Risk factors for coronavirus disease 2019 (COVID-19) death in a population cohort study from the Western Cape Province, South Africa. Clin Infect Dis 2021;73:e2005–10.

23 Bousquet G, Falgarone G, Deutsch D, et al. ADL-dependency. D-dimers, LDH and absence of anticoagulation are independently associated with one-month mortality in older inpatients with Covid-19. Aging 2020;12:11306–13.

24 Caumes D, Graft S, et al. Asthma and COPD are not risk factors for ICU stay and death in case of SARS-CoV2 infection. J Allergy Clin Immunol Pract 2021;9:160–169.

25 Carrasco-Sánchez FJ, López-Carronosa M, Dolores, Martinez-Marcos FJ, et al. Admission hyperglycaemia as a predictor of mortality in patients hospitalised with COVID-19 regardless of diabetes status: data from the Spanish SEMI-COVID-19 registry. Ann Med 2021;53:103–16.

26 Chachkhieli D, Soliman MY, Bara D, et al. Neurological complications in a predominantly African American sample of COVID-19 patients: predictors and outcomes during hospitalization. Clin Neurol Neurosurg 2020;197:106173.

27 Chang MC, Hwang J-M, Jeon J-H, et al. Fasting plasma glucose level independently predicts the mortality of patients with coronavirus disease 2019 infection: a multicenter, retrospective cohort study. Endocrinol Metab 2020;35:593–601.

28 Chilimuru S, Sun H, Alemam A, et al. Predictors of mortality in adults admitted with COVID-19: retrospective cohort study from New York City. West J Emerg Med 2020;21:779–84.

29 Ciardulo S, Zerbini F, Perra S, et al. Impact of diabetes on COVID-19-related hospitalization: a retrospective, observational study from northern Italy. J Endocrinol Invest 2021;44:843–50.

30 pp Coppelli A, Giannarelli R, Aragona M, et al. Hyperglycaemia at hospital admission is associated with severity of the prognosis in patients hospitalised for COVID-19: the Pisa COVID-19 study. Diabetes Care 2020;43:845–8.

31 Crouse A, Grimes T, Li P, et al. Metformin use is associated with reduced mortality in a diverse population with COVID-19 and diabetes. medRxiv 2020. doi:10.1101/2020.07.29.20164020. [Epub ahead of print: 31 Jul 2020].

32 Dennis JM, Mateen BA, Sonabend R, et al. Type 2 diabetes and COVID-19-Related mortality in the critical care setting: a national cohort study in England, March–July 2020. Diabetes Care 2021;44:50–7.

33 Desai A, Voza G, Paierdi S, et al. The role of anti-hypertensive treatment, comorbidities and early introduction of LMWH in the setting of COVID-19: a retrospective, observational study in northern India. Int J Cardiol 2021;324:249–54.

34 de Souza Silva GA, da Silva SP, da Costa MAS, et al. Sars-CoV-2-CoV: an observational study in two institutions. Autoimmune and feto-maternal development. J Gynecol Obstet Hum Reprod 2020;101846:101846.

35 Escalera-Antezana JP, Lizon-Ferruno NF, Maldonado-Alanoca A, et al. Risk factors for mortality in patients with coronavirus disease 2019 (COVID-19) in Bolivia: an analysis of the first 107 confirmed cases. Int J Endocr Jpn 2020;41:43–42.

36 Esme M, Koca M, Dikmeer A, et al. Older adults with coronavirus disease 2019: a nationwide study in turkey. J Gerontol A Biol Sci Med Sci 2021;76:e86–75.

37 Fernández-Cruz A, Ruiz-Antonín B, Muñoz-Gómez A, et al. A retrospective controlled outcomes study of the impact of glucocorticoid treatment in SARS-CoV-2 infection mortality. Antimicrob Agents Chemother 2020;64:e01168–20.
coronavirus disease 2019 (COVID-19) infection. *Clin Infect Dis* 2021;73:1–11.
73 Nachega JB, Ishoso DK, Otokoye JO, et al. Clinical characteristics and outcomes of patients hospitalized for COVID-19 in Africa: early insights from the Democratic Republic of the Congo. *Am J Trop Med Hyg* 2020;103:2419–28.
74 Nakashbandi M, Maini R, Daniel P, et al. The impact of obesity on COVID-19 complications: a retrospective cohort study. *Int J Obes* 2020;44:1832–7.
75 Anzola GP, Bertolamini C, Gregorini GA, et al. Neither ACEIs nor ARBs are associated with respiratory distress or mortality in COVID-19 results of a prospective study on a hospital-based cohort. *Intern Emerg Med* 2020;15:1477–84.
76 Nicholson CJ, Wooster L, Sigurisd H. Estimating risk of mechanical ventilation and mortality among adult COVID-19 patients admitted to mass General Brigham: the vice and dice scores. *medRxiv* 2020.
77 Nogueira PJ, de Araujo Nobre M, Costa A, et al. The role of health precautions on COVID-19 deaths in Portugal: evidence from surveillance data of the first 20293 infection cases. *J Clin Med* 2020;9:2368.
78 Pan W, Zhang J, Wang M, et al. Clinical features of COVID-19 in patients with essential hypertension and the impacts of renin-angiotensin-aldosterone system inhibitors on the prognosis of COVID-19 patients. *Hypertension* 2020;76:732–41.
79 Portolés J, Marques M, López-Sánchez P, et al. Chronic kidney disease and acute kidney injury in the COVID-19 Spanish outbreak. *Nephrol Dial Transplant* 2020;35:1353–61.
80 Rastad H, Karim H, Etaha H-S, et al. Risk and predictors of in-hospital mortality and renal impairment in patients with COVID-19 and cardiovascular disease. *Diabetologia Metab Syndr* 2020;12:57.
81 Recinella G, Marasco G, Serafini G, et al. Prognostic role of nutritional status in elderly patients hospitalized for COVID-19: a monocentric study. *Aging Clin Exp Res* 2020;32:2695–701.
82 Reiley M, Kristensen KB, Pottegård A, et al. Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort. *Int J Epidemiol* 2020;49:1488–81.
83 Rivera-Izquierdo M, Del Carmen Valero-Ubierna M, Delamo JL, et al. Sociodemographic and clinical characteristics on admission associated with COVID-19 mortality in hospitalized patients: a retrospective observational study. *PLoS One* 2020;15:e0235107.
84 Rodríguez-Molinero A, Gálvez-Barrón C, Miñarro A, et al. Association between COVID-19 prognosis and disease presentation, comorbidities, and chronic treatment of hospitalized patients. *PLoS One* 2020;15:e0239571.
85 Giorgi Rossi P, Marino M, Formisano D, et al. Characteristics and outcomes of a cohort of COVID-19 patients in the province of Reggio Emilia, Italy. *PLoS One* 2020;15:e0237227.
86 pp Rottoli M, Bernante P, Belvedere A, et al. How important is obesity as a risk factor for respiratory failure, intensive care admission and death in hospitalised COVID-19 patients? results from a single Italian centre. *Eur J Endocrinol* 2020;183:385–97.
87 Rozaiyani A, Savi F, Spanigon F, et al. Factors associated with death in COVID-19 patients in Jakarta, Indonesia: an epidemiological study. *Acta Med Indones* 2020;52:246–54.
88 Salacup G, Lo KB, Gul F, et al. Characteristics and clinical outcomes of COVID-19 patients in an underserved-inner City population: a single tertiary center cohort. *J Med Virol* 2021;93:416–23.
89 Salazar E, Christensen PA, Givass EA, et al. Treatment of coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol* 2020;190:2290–303.
90 Sands KE, Wenzel RP, McLean LE, et al. Patient characteristics and admitting vital signs associated with coronavirus disease 2019 (COVID-19)-related mortality among patients admitted with acute respiratory illness. *Am J Respir Crit Care Med* 2021;193:389–405.
91 Santos MM, Lucena EES, Lima KC, et al. Survival and predictors of deaths of patients hospitalised due to COVID-19 from a retrospective and multicentre cohort study in Brazil. *Epidemiol Infect* 2020;148:e198.
92 Sebastian J, Platt J, Cromer SJ, et al. Diabetes as a risk factor for poor early outcomes in patients hospitalized with COVID-19. *Diabetes Care* 2020;43:2938–44.
93 Shah P, Owens J, Franklin J, et al. Demographics, comorbidities and outcomes in hospitalized COVID-19 patients in rural Southwest Pennsylvania. *Am J Med* 2020;133:e153–60.
94 Li P, Chen L, Liu Z, et al. Clinical features and short-term outcomes of elderly patients with COVID-19. *Int J Infect Dis* 2020;97:245–50.
Yahyavi A, Hemmati N, Derakhshian P, et al. Angiotensin enzyme inhibitors and angiotensin receptor blockers as protective factors in COVID-19 mortality: a retrospective cohort study. Intern Emerg Med 2021;16:883–93.

Yan Y, Yang Y, Wang F, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Res Care 2020;8:e001343.

Yan Q, Zuo P, Cheng L, et al. Acute kidney injury is associated with in-hospital mortality in older patients with COVID-19. J Gerontol A Biol Sci Med Sci 2021;76:456–62.

Yazdianpanah Y, French COVID cohort investigators and study group. Impact on disease mortality of clinical, biological, and virological characteristics at hospital admission and overtime in COVID-19 patients. J Med Virol 2021;93:2149–59.

Zandkarimi E, Moradi G, Mohsenpour B. The prognostic factors affecting the survival of Kurdistan Province COVID-19 patients: a cross-sectional study from February to may 2020. Int J Health Policy Manag 2020. doi:10.34172/ijhpm.2020.155. [Epub ahead of print: 22 Aug 2020].

An C, Lin H, Kim D-W, et al. Machine learning prediction for mortality of patients diagnosed with COVID-19: a nationwide Korean cohort study. Sci Rep 2020;10:18716.

pp Beopuka BI, Mandina M, Makulo JR, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. JAMA 2020;323:324–502.

Tehrani S, Killander A, Ästrand P, et al. Risk factors for death in adult COVID-19 patients: frailty predicts fatal outcome in older patients. Int J Infect Dis 2021;102:415–21.

Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

Stroup DF, Berlin JA, Morton SC, et al. Meta-Analysis of observational studies in epidemiology: a proposal for reporting, meta-analysis of observational studies in epidemiology (moose) group. JAMA 2000;283:2069–71.

Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.

Schünemann HJ, Cello C, Aki EA, et al. Grade guidelines: 18. How ROBINS-I and other tools to assess risk of bias in non-randomized studies should be used to rate the certainty of a body of evidence. J Clin Epidemiol 2019;111:105–14.

DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–50.

Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1731.

Newcombe RG, Bender R. Implementing grade: calculating the risk difference from the baseline risk and the relative risk. Evid Based Med 2014;19:6–8.

Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301–9.

Hamling J, Lee P, Weitkunat R, et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. J Clin Epidemiol 2015;68:1193–8.

Bagnardi V, Zambon A, Quatto P, et al. Flexible meta-regression functions for modeling aggregate dose-response data, with an application to alcohol and mortality. Am J Epidemiol 2004;159:1077–86.

Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

Spiegelman D, Hertzmark E, Wand HC. Point and interval estimates of population attributable risks in cohort studies: examples and software. Cancer Causes Control 2007;18:571–9.

Moazzami B, Chaturvedi S, Kasaian A, et al. Metabolic risk factors and risk of Covid-19: a systematic review and meta-analysis. PLoS One 2020;15:e0243600.

Farsalinos K, Barbouni A, Poula K, et al. Current smoking, former smoking, and adverse outcome among hospitalized COVID-19 patients: a systematic review and meta-analysis. Ther Adv Chronic Dis 2021;10:24623309211035765.

Shastri MD, Shukla SD, Chong WC, et al. Smoking and COVID-19: what we know so far. Respir Med 2021;176:106237.

Noharia D, Lee K, Lee DS, et al. Mortality rate and predictors of mortality in hospitalized COVID-19 patients with diabetes. Health Care 2020;8:338.

Jackson BR, Gold JAW, Natarajan P, et al. Predictors at admission of mechanical ventilation and death in an observational cohort of adults hospitalized with COVID-19. Clin Infect Dis 2020;ciaa459.

Braude P, Carter B, Short R, et al. The influence of ACE inhibitors and ARBs on hospital length of stay and survival in people with COVID-19. Int J Cardiol Heart Vasc 2020;31:100660.

Cai Y, Shi S, Yang F, et al. Fasting blood glucose level is a predictor of mortality in patients with COVID-19 independent of diabetes history. Diabetes Res Clin Pract 2020;169:108437.

Hwang J-M, Kim J-H, Park J-S, et al. Neurological diseases as mortality predictive factors for patients with COVID-19: a retrospective cohort study. Neuroul Sci 2020;41:2317–24.

Williamson EJ, Walker AI, Shashkin K, et al. Factors associated with COVID-19-related death using Open SFLY. Nature 2020;584:430–6.
Bruce E, Barlow-Pay F, Short R, et al. Prior routine use of non-steroidal anti-inflammatory drugs (NSAIDs) and important outcomes in hospitalised patients with covid-19. J Clin Med 2020;9:2586.

Carillo-Vega MF, Salinas-Escudero G, Garcia-Peña C, et al. Early estimation of the risk factors for hospitalization and mortality by COVID-19 in Mexico. PLoS One 2020;15:e0238805.

Hernández-Galdamez DR, González-Bloczke Miguel Angel, Romo-Dueñas DK, et al. Increased Risk of Hospitalization and Death in Patients With COVID-19 and Pre-existing Noncommunicable Diseases and Modifiable Risk Factors in Mexico. Arch Med Res 2020;51:683–9.

Parra-Bracamont GM, López-Villalobos N, Parra-Bracamont FE. Clinical characteristics and risk factors for mortality of patients with COVID-19 in a large data set from Mexico. Ann Epidemiol 2020;52:93–8.

Wollenstein-Betz S, Cassandras CG, Paschalidis IC. Personalized predictive models for symptomatic COVID-19 patients using basic preconditions: hospitalizations, mortality, and the need for an ICU or ventilator. Int J Med Inform 2020;142:104589.

Hernández-Vásquez A, Azáhedeo D, Vargas-Fernández R, et al. Association of comorbidities with pneumonia and death among COVID-19 patients in Mexico: a nationwide cross-sectional study. J Prev Med Public Health 2020;53:211–9.

Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;5:802–10.

Mehra MR, Desai SS, Kuy S, et al. Factors associated with increased risk for hospitalization mortality in patients with COVID-19: a systematic review and meta-analysis comprising 18,506 patients. JAMA Intern Med 2021;31:17–26.

Palacios MR, Chamarro-Pareja N, Karamanis D, et al. Diabetes is associated with increased risk for in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis comprising 18,506 patients. JAMA Intern Med 2021;36:17–26.

Gaskell J, McGill N, Meyer SA, et al. Obesity is associated with increased risk for mortality among hospitalized patients with COVID-19. Obesity 2020;28:1806–10.

Poblador-Bou P, Carmona-Pinzón J, Isakeim-Skoufa I, et al. Baseline chronic comorbidity and mortality in Laboratory-Confirmed COVID-19 cases: results from the PRECOVID study in Spain. Int J Environ Res Public Health 2020;17:5171.

Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. Diabetes Care 2020;43:1382–91.

Sousa GJB, Garces TS, Cestari VRF, et al. Mortality and survival of COVID-19: Epidemiological Risk Factors. J Epidemiol 2020;33:e123.

Wide COVID-19 Research Consortium. Geospatial distribution and predictors of mortality in hospitalized patients with COVID-19: a cohort study. Open Forum Infect Dis 2020;7:e046388.

Talarvera B, García-Azorín D, Martínez-Piás E, et al. Anosmia is associated with lower in-hospital mortality in COVID-19. J Neurourol Neurosurg Psych 2020;142:104589.

Xie J, Zu Y, Alkhatib A, et al. Metabolic syndrome and COVID-19 mortality among adult black patients in New Orleans. Diabetes Care 2020;43:1382–91.

Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934–43.

Wu J, Huang J, Zhu G, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Res Care 2020;8:e001476.

Yang P, Wang N, Wang J, et al. Admission fasting plasma glucose is an independent risk factor for 28-day mortality in patients with COVID-19. J Med Virol 2021;93:2168–76.

Yu C, Lei Q, Li W, et al. Clinical characteristics, associated factors, and predicting COVID-19 mortality risk: a retrospective study in Wuhan, China. J Am Prev Med 2020;59:168–75.

Zhang J, Kong W, Xia P, et al. Impaired fasting glucose and diabetes are related to higher risks of complications and mortality among patients with coronavirus disease 2019. Front Endocrinol 2020;11:525.
Open access

190 Zhu L, She Z-G, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020;31:1068–77.

191 Zimering MB, Razazki T, Tsang T, et al. Inverse association between serotonin 2A receptor antagonist medication use and mortality in severe COVID-19 infection. Endocrinol Diabetes Metab J 2020;4:1–5.

192 Almazedi S, Al-Youna S, Jamal MH, et al. Characteristics, risk factors and outcomes among the first consecutively 1096 patients diagnosed with COVID-19 in Kuwait. Eclinicalmedicine 2020;24:100448.

193 Tourangou SH, Briggemann R, Linkens AEMJH, et al. Mortality and the use of antithrombotic therapies among nursing home residents with COVID-19. J Am Geriatr Soc 2020;68:1647–52.

194 Lopez-Mendez I, Aquino-Matus J, Gall SB-M, et al. Association of liver steatosis and fibrosis with clinical outcomes in patients with SARS-CoV-2 infection (COVID-19). Ann Hepatol 2021;20:100271.

195 Du R-H, Liang R-L, Yang C-Q, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020;55:2000524.

196 Movita SGM, Azad KAK, Kabir A, et al. Clinical profile of 100 confirmed COVID-19 patients admitted in Dhaka medical college Hospital, Dhaka, Bangladesh. Journal of Bangladesh College of Physicians and Surgeons 2020;29:36–9.

197 Sun H, Ning R, Tao Y, et al. Risk factors for mortality in 244 older adults with COVID-19 in Wuhan, China: a retrospective study. J Am Geriatr Soc 2020;68:1619–23.

198 Alamdar NM, Afaghi S, Rahimi FS, et al. Mortality risk factors among hospitalized COVID-19 patients in a major referral center in Iran. Tohoku J Exp Med 2020;252:73–84.

199 Hajifathalian K, Kumar S, Newberry C, et al. Obesity is associated with worse COVID-19 outcomes: an analysis of early data from New York City. Obesity 2020;28:1606–12.

200 Klang E, Kazim G, Soffer S, et al. Severe obesity as an independent risk factor for COVID-19 mortality in hospitalized patients younger than 50. Obesity 2020;28:1985–9.

201 Price-Haywood EJ, Burton J, Fort D, et al. Hospitalization and mortality among black patients and white patients with COVID-19. N Engl J Med 2020;382:2534–43.

202 Ramos-Rincón J-M, Buonaiuto V, Ricci M, et al. Clinical characteristics and risk factors for mortality in very old patients hospitalized with COVID-19 in Spain. J Gerontol A Biol Sci Med Sci 2021;76:e28–37.

203 Steinberg E, Wright E, Kushner B. In young adults with COVID-19, obesity is associated with adverse outcomes. West J Emerg Med 2020;21:752–5.

204 Zhang F, Xiong Y, Wei Y, et al. Obesity predisposes to the risk of higher mortality in young COVID-19 patients. J Med Virol 2020;92:2536–42.

205 Gazzaruso C, Mariani G, Ravetto C, et al. Lupus anticoagulant and mortality in patients hospitalized for COVID-19. J Thromb Thrombolysis 2021;52:85–91.

206 Mather JF, Seip RL, McKay RG. Impact of fatmodine use on outcomes of hospitalized patients with COVID-19. Am J Gastroenterol 2020;115:1617–23.

207 Anderson MR, Geleris J, Anderson DR, et al. Body Mass Index and Risk for Intubation or Death in SARS-CoV-2 Infection: A Retrospective Cohort Study. Ann Intern Med 2020;173:782–90.

208 Ferrando-Vivas P, Doidge J, Thomas K, et al. Prognostic factors for 30-day mortality in critically ill patients with coronavirus disease 2019; an observational cohort study. Crit Care Med 2021;49:102–11.

209 Gayam V, Chobofo MD, Mergani MA, et al. Clinical characteristics and predictors of mortality in African-Americans with COVID-19 from an inner-city community teaching hospital in New York. J Med Virol 2021;93:812–9.

210 Muñoz-Price LS, Nattinger AB, Rivera F, et al. Racial disparities in incidence and outcomes among patients with COVID-19. JAMA Netw Open 2020;3:e2021892.

211 Li G, Zhou C-L, Ba Y-M, et al. Nutritional risk and therapy for severe and critically COVID-19 patients: a multicenter retrospective observational study. J Clin Nutr 2021;40:2154–61.

212 Wang Z, Zheutlin A, Kao Y-H, et al. Hospitalised COVID-19 patients of the Mount Sinai health system: a retrospective observational study using the electronic medical records. BMJ Open 2020;10:e034441.

213 Baronio M, Freni-Serrantino A, Pinelli M, et al. Italian SARS-CoV-2 patients in intensive care: towards an identikit for subjects at risk? Eur Rev Med Pharmacol Sci 2020;24:9698–704.

214 Adrish M, Chilimuri S, Mantri N, et al. Association of smoking status with outcomes in hospitalized patients with COVID-19. BMJ Open Respir Res 2020;7:e000716.

215 Chen L, Yu J, He W, et al. Risk factors for death in 1859 subjects with COVID-19. Leukemia 2020;34:2173–83.

216 Zhang J-J, Cao Y-Y, Tan G, et al. Clinical, radiological, and laboratory characteristics and risk factors for severity and mortality of 289 hospitalized COVID-19 patients. Allergy 2021;76:533–50.
Alharthy A, Aletreby W, Faqihi F, et al. Clinical characteristics and predictors of 28-day mortality in 352 critically ill patients with COVID-19: a retrospective study. J Epidemiol Glob Health 2021;11:98.

Qin L, Li X, Shi J, et al. Gendered effects on inflammation reaction and outcome of COVID-19 patients in Wuhan. J Med Virol 2020;92:2684–92.

Wang Z-H, Shu C, Ran X, et al. Critically ill patients with coronavirus disease 2019 in a designated ICU: clinical features and predictors for mortality. Risk Manag Healthc Policy 2020;13:833–45.

Farrell RJ, O’Regan R, O’Neill E, et al. Sociodemographic variables as predictors of adverse outcome in SARS-CoV-2 infection: an Irish Hospital experience. Ir J Med Sci 2021;190:893–903.

Wang K, Zuo P, Liu Y, et al. Clinical and laboratory predictors of in-hospital mortality in patients with coronavirus Disease-2019: a cohort study in Wuhan, China. Clin Infect Dis 2020;71:2079–88.

Chen T, Dai Z, Mo P, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a Single-Centered, retrospective study. J Gerontol A Biol Sci Med Sci 2020;75:1788–95.

Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020;8:475–81.

Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab Syndr 2020;14:535–45.

Pranata R, Huang I, Lim MA, et al. Impact of cerebrovascular and cardiovascular diseases on mortality and severity of COVID-19: a systematic review, meta-analysis, and meta-regression. J Stroke Cerebrovasc Dis 2020;29:104949.

Shang L, Shao M, Guo Q, et al. Diabetes mellitus is associated with severe infection and mortality in patients with COVID-19: a systematic review and meta-analysis. Arch Med Res 2020;51:700–9.

Varikasuvu SR, Varshney S, Dutt N. Markers of coagulation dysfunction and inflammation in diabetic and non-diabetic COVID-19. J Thromb Thrombolysis 2021;51:941–6.

Maddaloni E, Buzzetti R, Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev 2020:e3321321.

Kermali M, Khalsa RK, Pillai K, et al. The role of biomarkers in diagnosis of COVID-19 - A systematic review. Life Sci 2020;254:117788.

Morra ME, Van Thanh L, Kamel MG, et al. Clinical outcomes of current medical approaches for middle East respiratory syndrome: a systematic review and meta-analysis. Rev Med Virol 2018;28:e1977.

Matsuyama R, Nishiura H, Kutsuna S, et al. Clinical determinants of the severity of middle East respiratory syndrome (MERS): a systematic review and meta-analysis. BMC Public Health 2016;16:1203.

Yang J, Hu J, Zhu C. Obesity aggravates COVID-19: a systematic review and meta-analysis. J Med Virol 2021;93:257–61.

Guh DP, Zhang W, Bansback N, et al. The incidence of comorbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 2009;9:88.

Semenzato L, Botton J, Drouin J, et al. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. Lancet Reg Health Eur 2021;8:100158.

Thakur B, Dubey P, Benitez J, et al. A systematic review and meta-analysis of geographic differences in comorbidities and associated severity and mortality among individuals with COVID-19. Sci Rep 2021;11:8562.

Dubey P, Thakur B, Reddy S, et al. Current trends and geographical differences in therapeutic profile and outcomes of COVID-19 among pregnant women - a systematic review and meta-analysis. BMC Pregnancy Childbirth 2021;21:247.