Unpacking post-covid symptoms

**ORIGINAL RESEARCH** Retrospective cohort study

**Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection**

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**Study question** What is the excess risk and relative hazards of developing new clinical sequelae after the acute phase of SARS-CoV-2 infection in adults aged 18-65?

**Methods** Individuals aged 18-65 with continuous enrolment in a large United States health plan from January 2019 to the date of a diagnosis of SARS-CoV-2 infection (index date) were identified. Three comparator groups were matched by propensity score to individuals infected with SARS-CoV-2: a 2020 group, an historical 2019 group, and an historical group with viral lower respiratory tract illness. More than 50 clinical sequelae were identified after the acute phase of infection (defined as the index date plus 21 days) with ICD-10 (International Classification of Diseases, 10th revision) codes. Excess risk of clinical sequelae in the four months after the acute phase of SARS-CoV-2 infection and hazard ratios with Bonferroni corrected 95% confidence intervals were calculated.

**Figure**

- **Risk difference for clinical sequelae**
  - **Hazard ratio for clinical sequelae**

Risk difference (per 100 individuals) and hazard ratios for the most common clinical sequelae in the SARS-CoV-2 versus the 2020 comparator group, UnitedHealth Group Clinical Discovery Database up to 31 October 2020. *Aggregate diagnosis includes all subdiagnoses listed in eTable 1 (see supplementary file on bmj.com). DVT=deep vein thrombosis; PE=pulmonary embolism."
Study answer and limitations 14% of individuals infected with SARS-CoV-2 (27 074 of 193 113) had at least one new type of clinical sequelae that required medical care after the acute phase of SARS-CoV-2 infection, which was 4.95% higher than in the 2020 comparator group. The risk for specific sequelae attributable to SARS-CoV-2 after the acute phase of infection was significantly greater (all P<0.001) than in the three comparator groups (2020, 2019, and viral lower respiratory tract illness groups). Significant risk differences because of SARS-CoV-2 infection ranged from 0.02 to 2.26 per 100 people (all P<0.001), and hazard ratios ranged from 1.24 to 25.65 compared with the 2020 comparator group. Misclassification of new diagnoses might have occurred with ICD-10 codes, biasing the study results toward the null.

What this study adds The results indicate an excess risk for new clinical sequelae after the acute phase of SARS-CoV-2 infection in individuals aged 18-65, including specific types of sequelae less commonly seen in those with other viral illnesses.

COMMENTARY Common, burdensome, and highly variable

Our understanding of long covid (also known as post-covid syndrome) has progressed considerably since the first follow-up of people discharged from hospital in 2020 after SARS-CoV-2 infection. People who were not admitted to hospital with covid-19 infection but who have enduring symptoms have driven the wider recognition of long covid symptoms, including organ impairment.

Much evidence comes from small, observational studies or surveys using different case definitions and sampling frames, resulting in a wide range of prevalence estimates. Larger surveys found that enduring symptoms were more often reported among people who had had covid-19 than among controls who had not, including reporting of cognitive deficits. However, reliance on self-reporting in many studies has been criticised by some commentators.

In this issue, Daugherty and colleagues used a large electronic records dataset to describe the prevalence and risks of post-covid sequelae in patients both admitted to hospital and in the community in the United States. Several studies have retrospectively reviewed ICD-10 codes in electronic health records, including a large study reporting that people admitted to hospital with covid-19 were 3.5 times more likely to be readmitted and 7.7 times more likely to die within five months of discharge than controls admitted to hospital without covid-19.

Researchers using US Department of Veterans Affairs databases found increased use of analgesics, antidepressants, antihypertensives, and oral hypoglycaemics in the six months after confirmed covid-19 compared with controls, and data from the US TriNetX electronic health records network showed that nearly 34% of people testing positive for SARS-CoV-2 had a neurological or psychiatric diagnosis in the following six months. Daugherty and colleagues found certain conditions were more commonly diagnosed after covid-19 than after other viral lower respiratory tract infections. The estimated 14% incidence of new diagnoses up to six months after SARS-CoV-2 infection is strikingly similar to the 13.7% incidence of self-reported symptoms lasting more than 12 weeks found by the UK Office for National Statistics.

While both studies report higher incidence in people admitted to hospital, new symptoms and diagnoses were also seen in those who remained at home. The absolute number of people reporting long covid symptoms will be higher in the community owing to the (at least) 10-fold difference in the numbers admitted to hospital and those who stayed at home.

Primary care clinicians should expect patients with mild initial infections to report long covid or post-covid symptoms just as frequently as those who were critically ill.

Late onset

In common with most studies, Daugherty and colleagues report that enduring symptoms are more common in women, those living with social deprivation, and those with pre-existing comorbidities. Importantly, they found that 10% of people developed new diagnoses requiring medical attention more than three weeks after the initial infection, with 4% developing more than one new diagnosis. This feature is well described by people with real life experience, who call it the “corona-coaster.” People who present with late onset symptoms (particularly those not admitted to hospital) report that some healthcare professionals do not associate symptoms with covid-19 and do not provide appropriate assessment and treatment.

It is too early to predict how long clinical sequelae will persist after covid-19, but these symptoms clearly create a major personal burden for many people, with some individuals experiencing difficulty...
returning to work and some unable to care for dependents. Long covid is also putting a strain on healthcare services, which have already been decimated by the pandemic. Identifying risk factors would facilitate triage and faster access to specialist care. However, one of the peculiarities of long covid is its non-linear progression, hampering attempts to predict who will develop particular symptoms and when. Risk factors differ for different new diagnoses, suggesting that a variety of mechanisms could be at play. Applying these risk factors to clinical practice will probably need long covid to be subdivided into more specific phenotypes.

Daugherly and colleagues’ analyses included people aged 18-65, and although symptom reporting is less common outside this age band, evidence is growing that children also experience long covid. In older adults, symptoms could be under-reported because of assumptions that they are due to ageing or comorbidities. Healthcare professionals should be alert to the possibility of long covid in anyone with confirmed or suspected covid-19. How to treat these longer term consequences is now an urgent research priority.

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Risk difference (per 100 individuals) for the most common clinical sequelae by subpopulation, UnitedHealth Group Clinical Discovery Database up to 31 October 2020.

*Aggregate diagnosis includes all subdiagnoses listed in eTable 1 (see supplementary file on bmj.com). DVT=deep vein thrombosis; PE=pulmonary embolism

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Funded by OptumLabs. See full paper on bmj.com for competing interests. The data are proprietary and are not available for public use but might be available under a data use agreement to confirm the findings of this study.
Effect of dexamethasone on complications after major non-cardiac surgery

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Study question What is the effect of dexamethasone on complications and all cause mortality after major non-cardiac surgery?

Methods This phase III, double blind, randomised controlled trial was conducted in 34 centres in France in adults older than 50 years undergoing major non-cardiac surgery with an expected duration of more than 90 minutes. Eligible participants were randomly assigned to receive either dexamethasone (0.2 mg/kg immediately after the surgical procedure, and on day 1) or placebo. Randomisation was stratified on the two prespecified criteria of cancer and thoracic procedure. The anticipated time frame for recruitment was 24 months. The primary outcome was a composite of complications and all cause mortality at 14 days after surgery.

Study answer and limitations Dexamethasone was not associated with a significant reduction in complications and all cause mortality at 14 days after major non-cardiac surgery: 101 of 595 participants (17.0%) in the dexamethasone group and 117 of 589 (19.9%) in the placebo group had complications or died (adjusted odds ratio 0.81, 95% confidence interval 0.60 to 1.08; P=0.15). Adverse events were reported in 288 of 613 participants (47.0%) in the dexamethasone group and 296 of 609 (48.6%) in the placebo group (P=0.46). The 95% confidence interval for the main result was, however, wide and does not exclude the possibility of important clinical effectiveness (odds ratio 0.81, 95% confidence interval 0.60 to 1.08; P=0.15).

What this study adds The findings suggest that dexamethasone has no overall benefit in reducing the incidence of complications and all cause mortality 14 days after major non-cardiac surgery.

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Trial registration ClinicalTrials.gov NCT03218553.

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