Australian Government

Chief Scientist

31 August 2020

The Hon Karen Andrews MP
Minister for Industry, Science and Technology
Parliament House
CANBERRA ACT 2600

CC:
The Hon Greg Hunt MP, Minister for Health
Dr Paul Kelly, Chief Medical Officer

Dear Minister

Please find attached a response to your request for an analysis of the available evidence to respond to your question:

> *What are the determinants of morbidity and mortality due to COVID-19, and are there sex-related differences?*

This rapid response has been prepared by the Rapid Research Information Forum that I Chair. The report synthesises the evidence base on this matter, has been informed by relevant experts and has been peer reviewed. Details of the authors and peer reviewers can be found in the Appendix.

I hope this document proves useful to you and your colleagues.

Yours sincerely,

Dr Alan Finkel AO FAA FTSE FAHMS
Australia's Chief Scientist

GPO Box 2013
Canberra ACT 2601
Australia

Telephone: +61 2 6102 9210
Facsimile: +61 2 6213 6558

Email: chief.scientist@chiefscientist.gov.au
Web: www.chiefscientist.gov.au

31 August 2020

This rapid research brief responds to the question:

What are the determinants of morbidity and mortality due to COVID-19, and are there sex-related differences?

- For this paper we analyse the factors that influence the risk of infection, the risk of severe disease requiring hospitalisation or intensive care unit (ICU) admission, and the risk of death.
- There is little evidence that biological differences, including age, sex and comorbidity, influence the risk of acquiring the infection.
- Age is the leading determinant of severe disease and death among people with COVID-19. The risk associated with age increases rapidly from the age of 40 years.
- Compared to females, males with COVID-19 are more likely to be hospitalised, more likely to be admitted to an ICU and more likely to die.
- Among people with COVID-19, many medical comorbidities, such as heart disease and chronic obstructive pulmonary disease, increase the risk of hospitalisation, ICU admission and death. However, some comorbidities, such as asthma, probably do not increase risks.
- Low socio-economic status increases both the risk of acquiring COVID-19 and the risk of developing severe disease once infected. Risk of severe disease once infected is probably mainly due to the prevalence of comorbidities that are associated with low socio-economic status.
- The data on prolonged morbidity of COVID-19 among survivors are not yet available. Therefore, the factors that predict a higher risk of prolonged morbidity, and the nature of these long-term effects, remain to be defined.

Determinants of morbidity and mortality

The overall determinants of morbidity (illness) and mortality from COVID-19 are both social (socio-economic status, occupation, and engagement with healthcare), and biological (sex, age, race and medical comorbidity). To date, the evidence suggests that biological characteristics do not change the risk of acquiring the disease, however, they do influence the risk of developing severe disease and death if the disease is acquired. It is important to note that there are some limitations on the available data, including the difficulty in calculating the case fatality rate – the proportion of infected people who died – due to differing access to testing and how mortality is able to be counted across different countries. Nonetheless, there is extensive evidence that suggests that biological characteristics, particularly age, influence the risk of developing severe disease and death.[1]

Age

Age is the most influential and consistent determinant of COVID-19 severity worldwide. In a study of over 17 million British primary care patients among whom there were nearly 11,000 COVID-19 deaths, individuals 80 years or older had a greater than 20-fold increased mortality risk compared to those aged 50–59 years.[2] Every decade of life after 40 years was associated with a significantly increased rate of mortality, even when statistically adjusted for other factors including the presence of age-related medical comorbidities. Similarly, amongst approximately 20,000 patients admitted to hospital with COVID-19 in the UK, age was a substantially stronger independent predictor of death than any medical comorbidity identified.[3]

In a study of nearly 1.8 million US cases of COVID-19 associated with 100,000 deaths, the case fatality rate among people with no medical comorbidities was 0.1% for people under 40 years, 0.4% for those aged 40 to 49, increasing incrementally through to nearly 30% in those aged 80 and over.[4] Australian data, although more limited, confirms the impact of age, with a case fatality rate that increases after the age of 50.[5]

While the case fatality rate is significantly higher in older people, many people infected with COVID-19 aged less than 40 nonetheless die of the disease. As of 19 August 2020 in the US there were over 4,600 deaths attributable to COVID-19 in people under 44 years old, out of a total number of nearly 177,000.[6,7] There are also early reports of long-term morbidity in young people who have recovered from the initial infection.[8,9]

Sex-related differences

While males and females acquire COVID-19 at similar rates, all reliable studies surveyed have found males to have a higher risk of severe disease and death once infected with COVID-19.[10–13] This is true across all age groups, and is mirrored by Australian data which show sex differences in case fatality rate are more pronounced when the disease is more severe.[10,14]

To some extent the increased risk of death in males may reflect differences in how the immune system responds to SARS-CoV-2, and a potential direct effect of male hormones.[15–19] Biological differences in the way males and females respond to treatment have also been observed. For example, in the RECOVERY trial, dexamethasone reduced mortality in males but not in females.[20]

Some of the male-specific risk is likely to be associated with sex-linked behavioural characteristics, including higher rates of smoking, alcohol use, obesity, and lower rates of engagement with healthcare.[21]

Sex hormones

There is mounting evidence that hormonal differences between males and females may underlie the elevated male risk of disease and death.[15,17] US dermatologists first noted that among males hospitalised with COVID-19, the frequency of male pattern baldness was atypically high.[22] This has led to a hypothesis that the progression of COVID-19 may involve male hormones (androgens), as high levels are known to be associated with baldness.[23] Although this association appears to suggest sex hormones might have a direct impact on patient outcomes, possible confounding explanations mean this association requires further evaluation before anti-androgen therapy could be recommended.

Comorbidities

Underlying medical conditions, or comorbidities, are also consistently reported as risk factors for severe illness and death, although which diseases carry the most significant risk and whether there is a difference between males and females for each comorbidity is not yet fully determined.

Comorbidities that increase risk of severe disease and death

In a meta-analysis of seven studies, chronic obstructive pulmonary disease was found to be associated with a more than five-fold increased risk of severe COVID-19 disease.[24] These data are consistent with the independent association observed in the UK between chronic respiratory disease (excluding asthma) and elevated COVID-19 mortality.[2]

Pre-existing chronic heart disease significantly increases the risk of COVID-19 mortality and this effect persisted even when other confounding co-variables, including sex, were controlled for.[2] Similar findings emerged from an analysis of over 2,000 Chinese COVID-19 patients and a meta-analysis of nine international studies comprising nearly 2,000 patients.[25,26]

Obesity is a significant risk factor for severe COVID-19, with various studies showing that obese patients are more likely to suffer severe disease and experience worse outcomes.[2,27–29] Similar, but less pronounced effects are reported in overweight patients.[30] Recent data suggest that the impact of obesity on COVID-19 outcomes is most noticeable in male patients.[31]

Limited data on COVID-19 and type 1 diabetes are available, however, reports from Belgium suggest that type 1 diabetes does not increase the rate of hospitalisation in COVID-19 patients.[32] Type 2 diabetes is associated with an increased risk of medical interventions, multiple organ injury and mortality in COVID-19 patients.[33] Among Type 2 diabetes patients, worse outcomes were observed in patients with poorly controlled blood glucose levels. This risk factor is therefore highly relevant to the estimated 500,000 Australians with undiagnosed type 2 diabetes.[34]

Numerous other comorbidities have been independently associated with COVID-19 mortality including but not limited to malignancy, liver disease, stroke, dementia, neurological disease, kidney disease, organ transplant and spleen disease.[2,4,35]

Comorbidities with unknown risk of severe disease and death

Asthma has attracted attention due to its prevalence and its effect on the lungs. However, the role of asthma in COVID-19 severity remains controversial with some studies suggesting a protective effect and others suggesting that asthma is associated with increased COVID-19 mortality or prolonged intubation in COVID-19 patients.[36–38] This discrepancy likely reflects the heterogeneity of asthma, which involves a complex array of different disease presentations and treatment regimens, as well as the fact that acute worsening of asthma symptoms and direct manifestations of COVID-19 can be challenging to differentiate clinically.[39]

Comorbidities with little or no risk of severe disease and death

The initial suggestions that smoking could be a protective factor for COVID-19 morbidity and mortality have not been supported by subsequent large observational studies.[40–43] Both current and former smoking were associated with a higher risk of COVID-19 hospital-related death in age and sex-adjusted data, although this effect was lost when analyses were adjusted for other confounding variables.[36]

The effect of hypertension (high blood pressure) is uncertain and contested, partly because most of the studies have not distinguished between treated and untreated hypertension, the type of treatment, or taken account of the magnitude of the disease.[2,44] On balance, mild or drug-controlled hypertension appears not to be a risk for severe COVID-19 disease.

Pregnancy

Early in the pandemic, there were concerns that pregnant females would be susceptible to severe disease, based on H1N1 influenza data.[45] However, subsequent analysis suggested that while COVID-19 infection may increase the incidence of preterm birth and caesarean delivery, morbidity in pregnant females is similar to that of non-pregnant females of similar age.[46–48] It appears that the passage of COVID-19 infection to the foetus, known as vertical transmission, is possible though uncommon.[49] It is not possible at this time to make an assessment on consequent foetal morbidity and mortality.[49]

Race

Data from the US and the UK highlight that racial minorities have been disproportionately affected by COVID-19.[50,51] This is likely to reflect the higher chance of infection due to the social determinants of health, including poorer access to healthcare.[52] Additionally, culturally and linguistically diverse groups experience a

higher incidence of disease severity once infected due to the higher prevalence of chronic disease in these populations.[50] Separating an independent biological effect of genetic variations associated with race from these confounding influences is methodologically challenging, but among black patients in the US there does appear to be an independent effect.[50] In the UK, the OpenSAFELY study found black and South Asian people had a higher than average chance of COVID-19 related death even after adjustment for factors including pre-existing medical conditions.[2] The contribution of social determinants to these figures remains unclear.

In Australia, considerable concern has been expressed for Aboriginal and Torres Strait Islander populations because of the potential for more rapid spread of disease (particularly within remote communities) because of increased likelihood of movement between communities for family and cultural reasons, their high rates of chronic disease, and the presence of social determinants associated with adverse health outcomes.[53,54] As of 19 July 2020, there were 99 confirmed cases of COVID-19 in Aboriginal and Torres Strait Islander persons, with none having required ICU admission and none having died.[55] There is insufficient data to determine whether Aboriginal or Torres Strait Islander race independently confers a difference in biological risk. In New Zealand, Māori and Pacific people had a lower incidence of reported cases during the first wave of the pandemic.[56] Any impact in terms of hospitalisation and death is yet to be reported.

Determinants of prolonged morbidity

Only one study has examined individual patient factors that increase the likelihood of non-lethal prolonged morbidity. This study observed 274 outpatients diagnosed with COVID-19 two to three weeks after testing.[6] Overall, 35% reported not having returned to their normal state of health, and age was a significant predictor of this outcome.[6] Fatigue (71%), cough (61%), and headache (61%) were symptoms most commonly reported.[6] Factors such as age ≥50 or reporting three or more chronic medical conditions were associated with approximately 2.3 times odds of not returning to normal health after adjusting for age, sex and race. Obesity and reporting a psychiatric condition were individually also associated with more than two-fold odds of prolonged morbidity.

The effects of socio-economic status

COVID-19 has a disproportionate effect on individuals according to socio-economic status.[2] It seems likely that, as with most other conditions, COVID-19 affects people in lower socio-economic groups more than those in higher ones. The effect of socio-economic status appears to be expressed through both the risk of acquiring COVID-19 and the severity of the disease once acquired.

Risk of acquiring COVID-19 is likely heightened for low socio-economic groups for the following reasons:[57–60]

- crowded housing and worse sanitation facilities
- more crowded neighbourhoods
- greater employment in public-facing occupations
- inability to work from home (e.g. supermarket and warehouse workers)
- insecure employment within households and communities, which can be an impediment to self-isolation
- first language other than English and not receiving public health advice in a format that can be easily understood.

COVID-19 morbidity and mortality are likely heightened for low socio-economic groups for the following reasons:[57–61]

- poorer access to medical care
- heightened stress (e.g. financial stress) weakening the immune system
- discrimination (or anticipation of discrimination) by medical practitioners
- greater prevalence of comorbidities associated with worse outcomes with COVID-19.

Conclusion

The COVID-19 pandemic has a potentially disproportionate effect on individuals according to a multitude of social and biological characteristics, due to differences in risk of acquiring the disease and in the severity of the disease once acquired. The independent effect of age on risk of death once COVID-19 is acquired is quantitatively more important than any single other factor, with increased risk beginning at age 40. Low socio-economic status increases both the risk of acquiring COVID-19 and, mainly due to the higher prevalence of comorbidities amongst such people, the risk of developing severe disease once infected. In attempting to minimise overall community risk, the interdependence of risk factors should be taken into account.

An important note on available COVID-19 research

Although current COVID-19 research is available through pre-print servers, many of these articles have not yet been peer reviewed (an imperative pillar of the scientific method) and the relatively short time length of the current outbreak has resulted in variable testing and reporting practices in different countries. As such, conclusions drawn need to be interpreted with caution. Pre-prints are marked with a § in the reference list.

The development of information detailing determinants of morbidity and mortality for COVID-19 is a rapidly evolving area of research with almost daily updates. This brief is accurate at the time of writing and may become out of date at a later time of reading. Consultation with the Australian Academy of Science is possible if the reader has questions.

APPENDIX

Lead author, contributing authors and peer reviewers of this rapid research report

Lead author

Professor Michael Reade AM, Professor of Military Surgery and Medicine, University of Queensland and Australian Defence Force Joint Health Command

Contributing authors

Dr Carinna Hockham, Research Fellow, The George Institute for Global Health

Professor Fran Baum AO FASSA FAHMS, Matthew Flinders Distinguished Professor, Southgate Institute for Health, Flinders University

Emeritus Professor Jennifer Graves AO FAA, La Trobe University

Dr Kirsty Short, Australian Research Fellow, Faculty of Science, University of Queensland

Dr Michael Maze FRACP, Senior Lecturer in Medicine, Respiratory Physician, University of Otago

Professor Robyn Norton AO FAHMS, Chair of Global Health, Faculty of Medicine, Imperial College London

Peer reviewers

Professor Don Nutbeam FAHMS, Professor of Public Health University of Sydney

Professor Katherine Kedzierska FAHMS, NHMRC Leadership Fellow and Dame Kate Campbell Fellow, The Peter Doherty Institute for Infection and Immunity, University of Melbourne

Professor Lisa Cameron, Professorial Research Fellow, Melbourne Institute of Applied Economic and Social Research, University of Melbourne

Professor Mark Woodward, Professor of Medical Statistics, The George Institute for Global Health, UNSW Sydney

Dr Margarita Moreno-Betancur, ARC DECRA Fellow, Clinical Epidemiology and Biostatistics Unit, University of Melbourne and Murdoch Children's Research Institute

Dr Sonya Bennett, Chair, Communicable Diseases Network Australia and Deputy Chief Health Officer, Queensland Health

Conflicts of interest declaration

This briefing incorporates input from Australian experts directly involved in investigating the determinants of morbidity and mortality of COVID-19. Many of these contributors are working with international partners and collaborators and have a strong understanding of the current global research and innovation landscape. The contributing authors and peer reviewers are drawn from a range of institutions, initiatives and fields, and collectively provide an independent and authoritative perspective on this topic.

Acknowledgements

The production of this rapid research report was supported by staff of the Australian Academy of Science: Dr Hayley Teasdale, Chris Anderson and Anna-Maria Arabia. Edited by Dr Elizabeth Finkel AM and Robyn Diamond.

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RAPID RESEARCH
INFORMATION FORUM

What are the determinants of morbidity and mortality due to COVID-19, and are there sex-related differences?

The Rapid Research Information Forum (RRIF) is a forum for rapid information sharing and collaboration within the Australian research and innovation sector. It is convened by Australia's Chief Scientist, Dr Alan Finkel AO FTSE FAA FAHMS, and its operations are led by the Australian Academy of Science.

RRIF provides a mechanism to rapidly bring together relevant multidisciplinary research expertise to address pressing questions about Australia's response to COVID-19, as they emerge.

RRIF enables timely responses to be provided to governments based on the best available evidence. RRIF also informs the Chief Scientist's interactions and collaboration with other national chief scientific advisers. It demonstrates the critical value of research and innovation in driving societal as well as economic progress now and into the future.

RRIF participants

- Australia's Chief Scientist (Chair)
- Australian Academy of Science (AAS)
- Australian Academy of Health and Medical Sciences (AAHMS)
- Australian Academy of Technology and Engineering (ATSE)
- Academy of the Social Sciences in Australia (ASSA)
- Australian Academy of the Humanities (AAH)
- Royal Society Te Apārangi (New Zealand)
- Australian Council of Learned Academies (ACOLA)
- State and Territory Chief Scientists and representatives
- Chief Science Advisor to the Government of New Zealand
- Scientific expert members of the National Science and Technology Council (NSTC)
- CSIRO
- Universities Australia (UA)
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This report has been enabled through the contribution of RRIF participants and support from Australian philanthropists.