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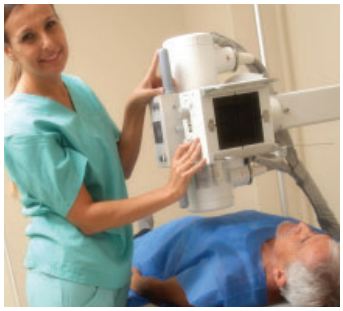

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ORIGINAL RESEARCH Systematic review and meta-analysis

Ionising radiation and cardiovascular disease

Little MP, Azizova TV, Richardson DB, et al

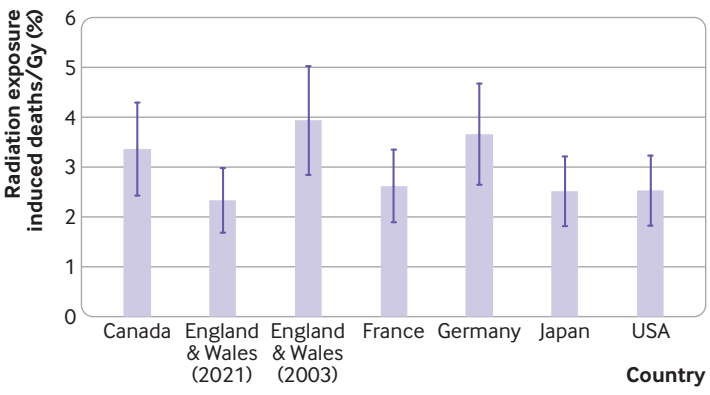
Cite this as: *BMJ* 2023;380:e072924
Find this at doi: 10.1136/bmj-2022-072924

Study question What are the radiation associated risks of cardiovascular disease (CVD) in groups exposed to radiation with individual radiation dose estimates?

Methods The main outcome was excess relative risk per unit dose (Gy), estimated by restricted maximum likelihood methods. Medline, Embase, Scopus, and Web of Science were searched on 6 October 2022, with no limits on date of publication or language.

Study answer and limitations 93 studies were included. Relative risk per Gy increased for all CVD (excess relative risk per Gy of 0.11 (95% confidence interval 0.08 to 0.14)) and for the four major subtypes of CVD (ischaemic heart disease, other heart disease, cerebrovascular disease, all other CVD). For ischaemic heart disease and all CVD, risks were larger per unit dose for lower dose (inverse dose effect) and for fractionated exposures (inverse dose fractionation effect). Population based excess absolute risks ranged from 2.33% per Gy (95% confidence interval 1.69% to 2.38%) for England and Wales to 3.66% per Gy (2.65% to 4.68%) for Germany, largely reflecting the underlying rates of CVD mortality in these populations. Estimated risk of mortality from CVD was generally dominated by cerebrovascular disease (around 0.94-1.25% per Gy), with the next largest contribution from ischaemic heart disease (around 0.30-1.20% per Gy). Although heterogeneity was noted between studies in this meta-analysis, it was noticeably reduced when analysis was restricted to higher quality studies or those at moderate doses (‹0.5 Gy) or low dose rates (‹5 mGy/h).

What this study adds Results provide evidence supporting a causal association between radiation exposure and CVD at high dose, and to a lesser extent at low dose, with some indications of differences in risk between acute and chronic exposures. The observed heterogeneity complicates a causal interpretation of these findings, although this heterogeneity was much reduced when only higher quality studies or those at lower doses or dose rates were considered.



Estimated excess absolute risk of death from radiation exposure (% per Gy) for all cardiovascular disease, for national populations (test dose=0.1 Gy). Whiskers represent 95% confidence intervals

Funding, competing interests, and data sharing See full paper on bmj.com for funding and competing interests. No additional data available.

Review registration
PROSPERO CRD42020202036.

Mental health and the covid-19 pandemic

ORIGINAL RESEARCH Evidence from a systematic review and meta-analysis of 134 cohorts

Comparison of mental health symptoms before and during the covid-19 pandemic

Sun Y, Wu Y, Fan S, et al

Cite this as: *BMJ* 2023;380:e074224
Find this at doi: 10.1136/bmj-2022-074224

Study question How much did mental health change during the covid-19 pandemic compared with pre-covid-19 levels in general populations and other population groups?

Methods A systematic review was conducted of studies comparing general mental health, anxiety symptoms, or depression symptoms assessed from 1 January 2020 or later with outcomes collected from 1 January 2018 to 31 December 2019 in any population, and comprising ≥90% of the same participants before and during the covid-19 pandemic or using statistical methods to account for missing data. Medline, PsycINFO, CINAHL, Embase, Web of Science, China National Knowledge Infrastructure, Wanfang, medRxiv, and Open Science Framework Preprints databases were searched for eligible studies. Restricted maximum likelihood random effects meta-analyses (worse covid-19 outcomes representing positive change) were performed. Risk of bias was assessed using an adapted Joanna Briggs Institute Checklist for Prevalence Studies.

Study answer and limitations As of 11 April 2022, 94 411 unique titles and abstracts including 137 unique studies from 134 cohorts were reviewed. Most of the studies were from high income (n=105, 77%) or upper middle income (n=28, 20%) countries. Among general population studies, no changes were found for general mental health (standardised mean difference (SMD)$_{change}$ 0.11, 95% confidence interval −0.00 to 0.22) or anxiety symptoms (0.05, −0.04 to 0.13), but depression symptoms worsened minimally (0.12, 0.01 to 0.24). Among women or female participants, general mental health (0.22, 0.08 to 0.35), anxiety symptoms (0.20, 0.12 to 0.29), and depression symptoms (0.22, 0.05 to 0.40) worsened by minimal to small amounts. In 27 other analyses across outcome domains among subgroups other than women or female participants, five analyses suggested that symptoms worsened by minimal or small amounts, and two suggested minimal or small improvements. No other subgroup experienced changes across all outcome domains. In three studies with data from March to April 2020 and late 2020, symptoms were unchanged from pre-covid-19 levels at both assessments, or increased initially then returned to pre-covid-19 levels. Substantial heterogeneity and risk of bias were present across analyses.

What this study adds High risk of bias in many studies and substantial heterogeneity suggest caution in interpreting results. Nonetheless, most symptom change estimates for general mental health, anxiety symptoms, and depression symptoms were close to zero and not statistically significant, and significant changes were of minimal to small magnitudes. Small negative changes occurred for women or female participants in all domains. The authors will update the results of this systematic review as more evidence accrues, with study results posted online (www.depressd.ca/covid-19-mental-health).

COMMENTARY New evidence suggests little deterioration in mental health linked to the pandemic

Whether or not the covid-19 pandemic was responsible for a secondary pandemic of poor mental health is a question posed repeatedly by scientists, the media, and the public. The answer has been elusive, despite a high volume of research—sometimes of inconsistent quality that encourages the cherry picking of findings to match preconceived hypotheses.

The systematic review by Sun and colleagues will help address these issues.[1] The authors included only studies that assessed participants' mental health both before and after the start of the pandemic. This means that the studies were not prone to selection biases related to the pandemic, at least at baseline assessments. The authors included results from an impressive 134 cohorts, mostly from high or upper middle income countries, looking at changes in general mental health, depression, and anxiety.

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So, what did we learn? The authors found no evidence in the general (not high risk) population of changes in general mental health, except for a slight deterioration in symptoms of depression. The word "slight" is important here. Sun and colleagues used a metric called the standardised mean difference, or SMD, and found a deterioration in depression symptoms of 0.12 SMD after the onset of the pandemic. Formally, this means a deterioration of 0.12 standard deviations.

Cohen, who invented the metric, developed it for randomised trials and estimated that SMD values less than 0.2 indicated a minimal effect, 0.2-0.5 a small effect, 0.5-0.8 a moderate effect, and 0.8 or more a large effect.[2] This may be too simplistic, however, and values between 0.24 and 0.5 have generally been suggested to correspond to a minimal clinically relevant difference for trials in people with depression.[3] Whether these cut-offs can be directly applied to general population studies, such as those in Sun and colleagues' systematic review, is not yet clear.

Meta-analyses of continuous general mental health, anxiety symptoms, and depression symptoms by population group

	General mental health			Anxiety symptoms			Depression symptoms		
	No of cohorts (No of participants)	Hedges g SMD* (95% CI)	I^2 (%)	No of cohorts (No of participants)	Hedges g SMD* (95% CI)	I^2 (%)	No of cohorts (No of participants)	Hedges g SMD* (95% CI)	I^2 (%)
General population	11 (30 185)	0.11 (−0.00 to 0.22)	97	4 (2632)	0.05 (−0.04 to 0.13)	37	4 (3470)	0.12 (0.01 to 0.24)	81
Women or females participants	6 (10 329)	0.22 (0.08 to 0.35)	91	5 (3500)	0.20 (0.12 to 0.29)	41	7 (3851)	0.22 (0.05 to 0.40)	89
Men or male participants	6 (11 546)	0.11 (−0.12 to 0.35)	98	4 (1271)	0.07 (−0.01 to 0.14)	0	7 (3905)	0.01 (−0.14 to 0.16)	82
Older adults	11 (9960)	−0.01 (−0.12 to 0.11)	93	6 (7193)	0.14 (−0.00 to 0.28)	93	7 (7419)	0.22 (0.06 to 0.38)	95
Young adults	2 (4221)	0.16 (−0.07 to 0.39)	96	2 (4602)	0.05 (−0.16 to 0.27)	95	4 (8043)	0.02 (−0.15 to 0.18)	96
University students	6 (6957)	0.00 (−0.17 to 0.17)	95	16 (12 642)	−0.07 (−0.21 to 0.06)	96	19 (26 164)	0.14 (0.01 to 0.26)	98
Children and adolescents	16 (11 505)	0.19 (−0.05 to 0.42)	99	8 (12 064)	0.02 (−0.12 to 0.16)	96	10 (11 679)	0.06 (−0.08 to 0.20)	96
Parents	3 (932)	0.39 (0.21 to 0.56)	57	1 (147)	0.25 (0.02 to 0.49)	—	5 (1639)	0.15 (−0.05 to 0.35)	87
People with pre-existing medical conditions	12 (6511)	0.10 (−0.01 to 0.20)	86	11 (5775)	0.08 (−0.04 to 0.21)	89	16 (21 594)	0.04 (−0.04 to 0.12)	90
People with pre-existing mental health conditions	2 (457)	−0.22 (−0.35 to −0.09)	0	3 (12 362)	0.12 (−0.11 to 0.35)	80	3 (12 352)	−0.05 (−0.08 to −0.03)	0
Medical staff	—	—	–	—	—	—	1 (180)	0.11 (−0.09 to 0.32)	—
People from sexual or gender minority groups	—	—	–	3 (3743)	0.23 (−0.09 to 0.54)	98	3 (3741)	0.19 (0.10 to 0.28)	67

CI=confidence interval; SMD=standardised mean difference.
*Positive effect sizes indicate worse mental health during covid-19 pandemic compared with pre-covid-19.

Funding, competing interests, and data sharing The study was funded by the Canadian Institutes of Health Research and McGill Interdisciplinary Initiative in Infection and Immunity Emergency COVID-19 Research Fund. No competing interests declared. Study data and statistical codes are available via the Open Science Framework (https://osf.io/96csg/).
Review registration PROSPERO CRD42020179703.

Beyond the pandemic

Interestingly, studies with several follow-up measures during 2020 (during the pandemic) suggested a sort of shock effect on mental health at the beginning of the pandemic, which in most studies stabilised to pre-pandemic levels later in 2020 or 2021.[4 5] Thus, the timing of assessments during the pandemic might have an influence on findings.

Accounting for period trends is also important: the reported minimal worsening in depression symptoms might have occurred even without the pandemic. Sun and colleagues' study is unable to rule out this possibility as it did not include a control period (for example, repeated measurements at times unrelated to the pandemic). A few individual studies reported increases in depression, anxiety, and psychiatric hospital admissions that began before the pandemic.[6-9]

Some individuals or subgroups might experience larger deteriorations than the population mean. The authors identify women as a vulnerable subgroup for depression, anxiety, and general mental health, although deteriorations were still minimal or small on average. Media attention has often focused on the pandemic's particular impact on young people, but this is not borne out by the present study: parameters of anxiety, depression, and general mental health did not deteriorate significantly in young adults, adolescents, or children. Future updates of this systematic review, which the authors will post online as more evidence accrues (www.depressd.ca/covid-19-mental-health), could usefully examine other subgroups, such as socially marginalised individuals.

There is a strong need to provide preventive mental health interventions for those most at risk of poor mental health outcomes

What does Sun and colleagues' review not tell us? First of all, it does not tell us why any deteriorations occurred. Was it the uncertainty of living through a poorly understood infectious disease, or linked to pandemic restrictions such as school and workplace closures, or caused by relatives becoming ill with covid-19, or the risk or experience of losing one's job? Or might these deteriorations have occurred even if the pandemic had not occurred, signifying an underlying, but not covid-19 related, pan-societal problem? Further research is required to help answer these important questions.

Finally, while the present study clearly shows that we need not be overly concerned about the general population's mental health in relation to the covid-19 pandemic, reported prevalence rates of mental health symptoms, especially among adolescents, are still concerningly high.[10-12] Pandemic or not, there is a strong need to provide preventive mental health interventions for those most at risk of poor mental health outcomes.

Cite this as: *BMJ* 2023;380:p435

Find the full version with references at http://dx.doi.org/10.1136/bmj.p435

Molnupiravir and risk of hospital admission or death in adults with covid-19

Xie Y, Bowe B, Al-Aly Z

Cite this as: *BMJ* 2023;380:e072705
Find this at doi: 10.1136/bmj-2022-072705

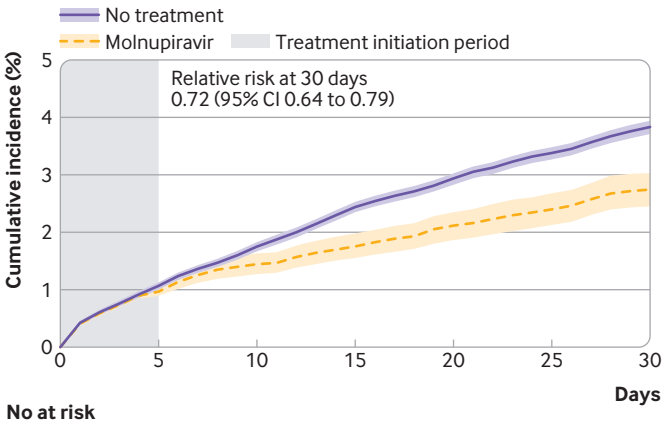
Study question Does treatment with molnupiravir reduce hospital admission or death at 30 days in adults with SARS-CoV-2 infection in the community at high risk of severe covid-19?

Methods This study emulated a randomised target trial using electronic health records from the US Department of Veterans Affairs. Participants comprised 85 998 adults with SARS-CoV-2 infection between 5 January and 30 September 2022 with at least one risk factor for progression to severe covid-19: age ›60 years, body mass index ›30, chronic lung disease, cancer, diabetes, cardiovascular disease, and chronic kidney disease. 7818 participants were eligible for and treated with molnupiravir and 78 180 received no treatment. The primary outcome was a composite of hospital admission or death at 30 days. The clone method with inverse probability of censoring weighting was used to adjust for informative censoring and balance baseline characteristics between the groups. The cumulative incidence function was used to estimate the relative risk and the absolute risk reduction at 30 days.

Study answer and limitations Molnupiravir was associated with a reduction in hospital admission or death at 30 days (relative risk 0.72 (95% confidence interval 0.64 to 0.79)) compared with no treatment; the event rates for hospital admission or death at 30 days were 2.7% (95% confidence interval 2.5% to 3.0%) for molnupiravir and 3.8% (3.7% to 3.9%) for no treatment; the absolute risk reduction was 1.1% (95% confidence interval 0.8% to 1.4%). Molnupiravir appeared to be effective in those who had not been vaccinated against covid-19 (relative risk 0.83 (0.70 to 0.97) and absolute risk reduction 0.9% (0.2% to 1.9%)), had received one or two vaccine doses (0.69 (0.56 to 0.83) and 1.3% (0.7% to 1.9%)), and had received a booster dose (0.71 (0.58 to 0.83) and 1.0% (0.5% to 1.4%)); in those infected during the era when the omicron subvariant BA.1 or BA.2 was predominant (0.72 (0.62 to 0.83) and 1.2% (0.7% to 1.6%)) and when BA.5 was predominant (0.75 (0.66 to 0.86) and 0.9% (0.5% to 1.3%)); and in those with no history of SARS-CoV-2 infection (0.72 (0.64 to 0.81) and 1.1% (0.8% to 1.4%)) and with a history of SARS-CoV-2 infection (0.75 (0.58 to 0.97) and 1.1% (0.1% to 1.8%)). The composition of the study participants—most were white and men—might limit the generalisability of the results.

What this study adds The findings of this emulation of a randomised target trial suggest that molnupiravir can reduce hospital admission or death at 30 days in adults with SARS-CoV-2 infection in the community during the omicron predominant era who are at high risk of progression to severe covid-19 and eligible for treatment with molnupiravir.

Funding, competing interests, and data sharing Funded by the US Department of Veterans Affairs. No competing interests declared. Veterans Affairs data are made freely available to researchers behind a firewall with an approved Veterans Affairs study protocol. For more information, please visit https://www.virec.research.va.gov or contact VIReC@va.gov.



No at risk				
No treatment	78 180	73 823	72 740	70 243
Molnupiravir	7818	7635	7554	7155
Cumulative No of events				
No treatment	0	1305	2191	2850
Molnupiravir	0	127	196	262

Cumulative incidence of hospital admission or death in molnupiravir (purple) and no treatment (orange) groups. Shaded area denotes treatment initiation period. Shading represents 95% confidence interval (CI)