research

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ORIGINAL RESEARCH Time stratified case crossover study

Ambient heat and risks of emergency department visits among adults in the United States

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Cite this as: *BMJ* 2021;375:e065653
Find this at doi: 10.1136/BMJ-2021-065653

Study question Are days of extreme heat associated with a higher risk of emergency department visits for any cause or cause specific conditions in the conterminous United States among adults with health insurance?

Methods The study sample comprised 74.2 million commercial and Medicare Advantage beneficiaries across the US aged 18 years or older between May and September (warm season) 2010-19. Time stratified case crossover analyses with distributed lag non-linear models were used to estimate the association between warm season ambient temperature and cause specific emergency department visits.

Study answer and limitations 21 996 670 emergency department visits for any cause were recorded in the study period. Days of extreme heat (defined as the 95th centile of the local warm season temperature distribution) were associated with a 7.8% (95% confidence interval 7.3% to 8.2%) excess relative risk of emergency department visits for any cause, 66.3% (60.2% to 72.7%) for heat related illnesses, 30.4% (23.4% to 37.8%) for renal disease, and 7.9% (5.2% to 10.7%) for mental disorders. Days of extreme heat were associated with an excess absolute risk of emergency department visits for heat related illness of 24.3 (95% confidence interval 22.9 to 25.7) per 100 000 people at risk per day. Heat was not associated with a higher risk of emergency department visits for cardiovascular or respiratory diseases. This study was limited to adults with health insurance, and so the results might not be generalisable to other populations.

Excess relative risk and excess absolute risk of cause specific emergency department (ED) visits associated with extreme temperature over lag days 0-5 in 2939 US counties, 2010-19*

	Average extreme heat (34.4°C)	
Reason for ED visits	Excess relative risk (%)	Excess absolute risk (No/100 000 people at risk/day)
Any cause	7.8 (7.3 to 8.2)	8.4 (7.9 to 8.8)
Heat related illness	66.3 (60.2 to 72.7)	24.3 (22.9 to 25.7)
Renal disease	30.4 (23.4 to 37.8)	14.7 (12.1 to 17.4)
Cardiovascular disease	−2.2 (−3.7 to −0.6)	−1.5 (−2.7 to −0.4)
Respiratory disease	−5.0 (−6.5 to −3.4)	−3.9 (−5.1 to −2.6)
Mental disorders	7.9 (5.2 to 10.7)	5.9 (4.0 to 7.9)
Negative control: epilepsy	−3.3 (−11.2 to 5.3)	−2.7 (−9.7 to 4.2)

*Extreme heat was defined based on the 95th centiles of local county specific temperature distribution during the warm season, and excess risks are expressed versus the local first centile.

What this study adds Days of extreme heat are associated with a higher risk of emergency department visits for any cause, heat related illness, renal disease, and mental disorders among both younger and older adults.

Funding, competing interests, and data sharing Supported by the US National Institutes of Health/National Institute of Environmental Health Sciences and the Wellcome Trust. No competing interests declared. No additional data available.

Developing trustworthy guidelines

ORIGINAL RESEARCH Empirical analysis

Discordant and inappropriate discordant recommendations in consensus and evidence based guidelines

Yao L, Ahmed MM, Guyatt GH, et al

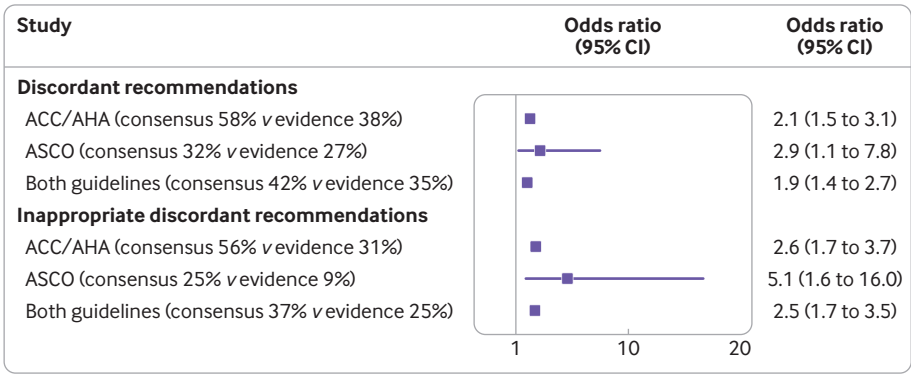
Cite this as: *BMJ* 2021;375:e066045

Find this at doi: 10.1136/BMJ-2021-066045

Study question Does the alignment of strength of recommendations with quality of evidence differ in consensus based versus evidence based guidelines?

Methods Recommendations in guidelines developed by the American College of Cardiology and the American Heart Association (ACC/AHA) and the American Society of Clinical Oncology (ASCO) using consensus based or evidence based methods were included. The number of discordant recommendations (strong recommendations with low quality evidence) and inappropriate discordant recommendations (those that did not meet grading of recommendations assessment, development, and evaluation criteria of appropriateness) were extracted. Odds ratios were used to estimate discrepancies between consensus based and evidence based guidelines.

Study answer and limitations Of recommendations based on low quality evidence, using the consensus based approach, ACC/AHA issued strong recommendations for 58% (n=115), versus 38% (n=117) using the evidence based approach (odds ratio 2.1, 95% confidence interval 1.5 to 3.1) , and ASCO issued 32% (n=92) that proved discordant by a consensus based approach versus 27% (n=30) by evidence based methods (odds ratio 2.9, 95%



Proportion of discordant recommendations and inappropriate discordant recommendations in consensus versus evidence based methods of guidelines development. Odds ratio >1 indicates that guidelines developed by consensus based methods generate more discordant or inappropriate discordant recommendations than the guidelines that employ evidence based approaches. ACC/AHA=American College of Cardiology and American Heart Association; ASCO=American Society of Clinical Oncology

OPINION Liang Yao, Gordon H Guyatt, and Benjamin Djulbegovic

Can we trust strong recommendations based on low quality evidence?

A necessary requirement for development of trustworthy guidelines is to respect the relation between the quality (certainty) of evidence and strength of recommendations. Strong recommendations are justified when they are based on high quality evidence, because such recommendations are considered more accurate. On the other hand, uncertainty in benefits and harms (that is, low quality evidence) generally leads to weaker recommendations.

The failure to recognise this important principle results in a tendency to issue strong recommendations based on low quality evidence (which we call discordant recommendations), often leading to harm. For instance, based on advice from low quality evidence, women have experienced avoidable adverse effects from hormone replacement therapy prescribed for the prevention of cardiovascular disease; and women with breast cancer have undergone highly toxic stem cell transplantation without benefit. This practice of decoupling the quality of evidence from the strength of recommendations is usually justified by separating guidelines into consensus based guidelines versus evidence based guidelines—a practice that does not appear to have abated over time.

Basing treatment decisions or clinical guidelines on low quality evidence means that the true effects of a treatment or clinical decision might differ considerably from best estimates. This discrepancy could result in launching campaigns (such as those designed to persuade women to use hormone replacement therapy) that are based on an unjustified faith in net benefit instead of transparently sharing the uncertainties in the quality of evidence on which the recommendations were based. Inappropriately strong recommendations have other problematic consequences, such as discouraging future randomised controlled trials that would generate higher quality evidence.

However, not all discordant recommendations are equally problematic. For instance, patients with a high likelihood of bad outcomes might all be willing to try an unproven, but potentially beneficial intervention.

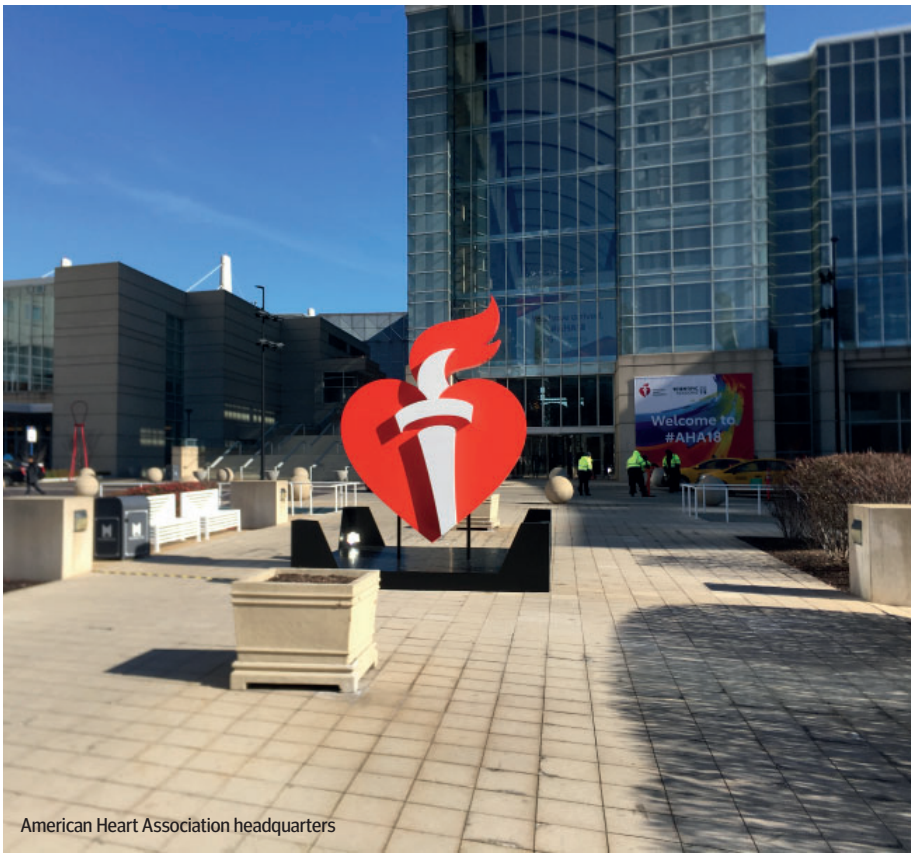
confidence interval 1.1 to 7.8). The odds ratio of consensus based versus evidence based approach for ACC/AHA and ASCO guidelines combined was 1.9 (1.4 to 2.7). The consensus based approach generated 2.6 times higher odds of more inappropriate discordant recommendations over evidence based guidelines in ACC/AHA guidelines (odds ratio 2.6, 95% confidence interval 1.7 to 3.7) and 5.1 times greater odds in ASCO guidelines (5.1, 1.6 to 16.0). The odds ratio of consensus based versus evidence based approach for ACC/AHA and ASCO guidelines combined was 2.5 (1.7 to 3.5). One limitation of this study is that a detailed assessment of evidence quality to verify the authors' rating of quality of evidence was not carried out.

What this study adds Results suggest that consensus based guidelines generate more inappropriate strong recommendations than evidence based guidelines.

Funding, competing interests, and data sharing
This project was supported in part by grant number R01HS024917 from the Agency for Healthcare Research and Quality.

No competing interests declared.

No additional data available.



American Heart Association headquarters

Issuing discordant recommendations without a compelling rationale is not unusual. The problem has previously been highlighted by the World Health Organization and Endocrine Society, and most recently in our study in *The BMJ*. We found that when the American College of Cardiology (ACC)/American Heart Association (AHA) and the American Society of Clinical Oncology (ASCO) (the two largest worldwide organisations that develop guidelines for heart disease and cancer, the two leading causes of death globally) faced low quality evidence, 41% and 20% of their recommendations proved to be inappropriate

Issuing discordant recommendations without a compelling rationale is not unusual

or discordant, respectively. Inappropriate discordant recommendations are those that do not meet the GRADE (grading of recommendations assessment, development, and evaluation) criteria of appropriateness. Although these leading organisations claim to use evidence based methods for their guidelines, the fact that up to 41% of their recommendations are inappropriate and discordant should raise concerns in both health professionals and patients.

Some organisations—including the ACC/AHA and ASCO—explicitly classify their guidelines as evidence based when much of the supporting evidence is deemed to be moderate or high quality, and classify their guidelines as consensus based when they are not. In their consensus versus evidence based guidelines, the odds of issuing inappropriate discordant recommendations proved 2.6 times higher in ACC/AHA guidelines and 5.1 times higher in ASCO guidelines. Classifying guidelines as consensus based might allow panels to be less rigorous in ensuring that the strength of recommendations is consistent with the underlying quality of evidence. All guidelines require judicious consideration of the relevant evidence—in other words, all guidelines should be evidence based—and organisations should focus on avoiding inappropriate discordant recommendations.

When facing low or very low quality evidence, guidelines should avoid issuing inappropriate discordant recommendations. Abandoning consensus based guidelines is likely to facilitate this goal.

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Cite this as: *BMJ* 2021;375:n2833

Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection

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Cite this as: *BMJ* 2021;375:e067873
Find this at doi: 10.1136/BMJ-2021-067873

Study question Is the risk of covid-19 associated with the time elapsed since the second dose of the Pfizer-BioNTech BNT162b2 mRNA vaccine, in people who received two doses?

Methods This retrospective study was performed in a large state mandated healthcare organisation in Israel, following the test negative study design. Participants (n=83 057) were aged ≥18 years and had a reverse transcription polymerase chain reaction (RT-PCR) test between 15 May 2021 and 17 September 2021, after two vaccine doses, and had no history of covid-19 infection. The main outcome was a positive RT-PCR test result. Individuals who tested positive for SARS-CoV-2 and controls were matched for week of testing, age category, and demographic group (ultra-orthodox Jews, individuals of Arab descent, and the general population). Further adjustment was made for age, sex, socioeconomic status, and comorbid conditions.

Study answer and limitations 7973 (9.6% of 83 057) adults had a positive SARS-CoV-2 test result on RT-PCR during the study period. Time elapsed since the vaccine dose was significantly longer in individuals who tested positive (P<0.001). The adjusted odds ratio for infection 90 days or more since vaccination were significantly increased compared with the reference of ≤90 days: 2.37 for 90-119 days, 2.66 for 120-149 days, and 2.82 for ≥150 days (P<0.001 for each 30 day interval). Owing to the observational study design, the potential for unmeasured confounders could affect the observed risk.

What this study adds The risk of SARS-CoV-2 infection in adults who received two doses of BNT162b2 vaccine increased with time elapsed since vaccination, compared with the reference (individuals vaccinated in the past 90 days).

Funding, competing interests, and data sharing This research was internally funded by Leumit Health Services and supported in part by the Intramural Research Program, Centre for Cancer Research, National Cancer Institute, National Institutes of Health. No competing interests declared. No additional data available.

Adjusted odds ratios for risk of SARS-CoV-2 in matched cohort

	Adjusted odds ratio (95% CI)	P value
Time since second vaccine (days):		
21-89	Reference	—
90-119	2.37 (1.67 to 3.36)	<0.001
120-149	2.66 (1.94 to 3.66)	<0.001
150-179	2.82 (2.07 to 3.84)	<0.001
≥180	2.82 (2.07 to 3.85)	<0.001
Age (continuous in years)	1.01 (1.00 to 1.01)	0.008
Male sex	1.05 (0.99 to 1.11)	0.08
Socioeconomic status (continuous 1-20)	0.97 (0.96 to 0.98)	<0.001

Based on a conditional regression model fitted in a cohort matched for week of testing, age category (<18-39, 40-59, ≥60 years), and demographic group.