research

Secondary mitral regurgitation in patients with heart failure p 17

Effect of food based interventions for adults with migraine p 18

SARS-CoV-2 B.1.1.7 variant and risk of hospital admission p 20

ORIGINAL RESEARCH Observational cohort study

Burden, treatment use, and outcome of secondary mitral regurgitation across the spectrum of heart failure

Bartko PE, Heitzinger G, Pavo N, et al

Cite this as: *BMJ* 2021;373:n1421

Find this at: http://dx.doi.org/10.1136/bmj.n1421

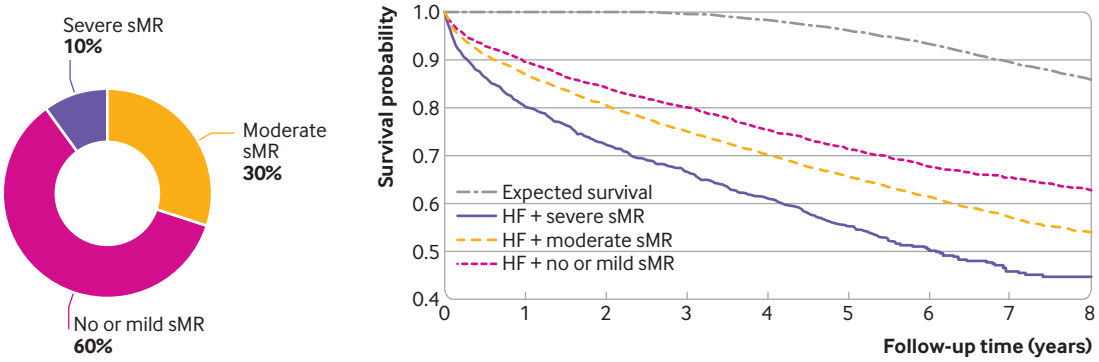
Study question What proportion of patients across the heart failure spectrum are affected by secondary mitral regurgitation (sMR), what types of treatment are used, and what are the outcomes?

Methods Observational cohort study of 13 332 patients with heart failure according to guideline diagnostic criteria. Data from the Viennese community healthcare provider network between 2010 and 2020 were used and individual patients were categorised into one of three subtypes of heart failure: reduced ejection fraction, mid-range ejection fraction, and preserved ejection fraction. The primary outcome was all cause mortality.

Study answer and limitations Severe sMR was diagnosed in 1317 patients (10.0%) and occurred across the entire spectrum of heart failure, being found in 656 (25.0%) of 2619 patients with reduced ejection fraction, 330 (10.2%) of 3242 with mid-range ejection fraction, and 331 (4.5%) of 7362 with preserved ejection fraction. Mortality of patients with severe sMR was higher than expected for people of the same age and sex in the same community (hazard ratio 7.53, 95% confidence interval 6.83 to 8.30, P<0.001). Compared with patients with heart failure and no or mild sMR, mortality increased stepwise with a hazard ratio of 1.29 (1.20 to 1.38, P<0.001) for moderate sMR and 1.82 (1.64 to 2.02, P<0.001) for severe sMR. Despite available state-of-the-art healthcare, severe sMR was rarely treated by surgical valve repair (6.9%) or replacement (4.7%); low risk transcatheter repair (3.6%) was similarly seldom used. A potential limitation of the study was that undiagnosed heart failure, and therefore sMR, was not considered.

What this study adds sMR is highly prevalent among patients with heart failure, and no subgroup with reduced, mid-range, or preserved ejection fraction is spared. Severe sMR is associated with excessive mortality. Specific treatment such as surgery and transcatheter mitral valve repair are rarely used.

Funding, competing interests, and data sharing This work was supported by a grant from the Austrian Science Fund (FWF No KLI-818B). See full paper on bmj.com for competing interests. No additional data available.



Prevalence and adverse outcome of patients with secondary mitral regurgitation (sMR) across the spectrum of heart failure (HF)

Dietary omega 3 fatty acids for migraine

ORIGINAL RESEARCH Randomised controlled trial

Dietary alteration of n-3 and n-6 fatty acids for headache reduction in adults with migraine

Ramsden CE, Zamora D, Faurot KR, et al

Cite this as: *BMJ* 2021;374:n1448
Find this at: http://dx.doi.org/10.1136/bmj.n1448

Study question Can food based interventions alter lipid mediators of pain and decrease headaches?

Methods In this parallel group, modified double blind, controlled trial, 182 adults with chronic and episodic migraine were randomly allocated to one of three diets for 16 weeks: H3 (increased eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA); H3-L6 (increased EPA+DHA, reduced linoleic acid), or a control diet (average US intake of n-3 and n-6 fatty acids). The primary endpoints (week 16) were the antinociceptive mediator 17-hydroxydocosahexaenoic acid (17-HDHA) in blood and a six item questionnaire assessing headache impact on quality of life (HIT-6).

Study answer and limitations The H3-L6 and H3 diets increased circulating 17-HDHA (log ng/mL) compared with the control diet (mean difference 0.6, 95% confidence interval 0.2 to 0.9, and 0.7, 0.4 to 1.1, respectively). The improvement in HIT-6 scores in the H3-L6 and H3 groups was not statistically significant (−1.6, −4.2 to 1.0, and −1.5, −4.2 to 1.2, respectively). Compared with the control diet, the H3-L6 and H3 diets decreased total headache hours per day, moderate to severe headache hours per day, and headache days per month. The H3-L6 diet decreased headache days per month more than the H3 diet (−2.0, −3.2 to −0.8). The role of the unblinded dietitian in this study was a limitation.

What this study adds The H3-L6 and H3 interventions altered headache related biochemical mediators and decreased headaches, but did not significantly improve quality of life.

COMMENTARY At last, grounds for optimism among those seeking a dietary option

Although the idea that diet contributes to migraine is nearly ubiquitous, few studies have shown the effectiveness of dietary interventions for migraine.[4 5] A recent systematic review found the most robust evidence for individualised diets eliminating foods associated with high immunoglobulin G reactivity, but this level of individualisation is difficult to achieve in clinical practice. The study by Ramsden and colleagues now provides good evidence that a diet rich in omega 3 (n-3) fatty acids reduces headache frequency compared with a diet with normal intake of omega 3 and omega 6 (n-6) fatty acids.[6]

Omega 3 and omega 6 fatty acids are precursors to oxylipins, which are involved in the regulation of pain and inflammation. Omega 3 fatty acid derivatives are associated with antinociceptive and anti-inflammatory effects, while oxylipins derived from omega 6 fatty acids worsen pain and provoke migraine in experimental models. Previous studies evaluating omega 3 fatty acid supplementation for migraine have been inconclusive.[7]

Ramsden and colleagues hypothesised that diets with higher levels of omega 3 fatty acids would increase serum 17-hydroxydocosahexaenoic acid (17-HDHA), an antinociceptive derivative,

Rebecca Burch rburch@bwh.harvard.edu
See bmj.com for author details

These results support recommending a high omega 3 diet to patients in clinical practice

and reduce headache related disability as measured by the six item headache impact test (HIT-6). In this randomised controlled trial, 182 participants were assigned to one of three diets. The control diet included typical levels of omega 3 and omega 6 fatty acids. Both intervention diets raised omega 3 fatty acid intake. One kept omega 6 linoleic acid intake the same as the control diet, and the other concurrently lowered linoleic acid intake.

Both intervention diets increased 17-HDHA levels, but HIT-6 scores were not statistically significantly different from the control group. Headache frequency was statistically significantly decreased in both intervention groups however. The high omega 3 diet was associated with a reduction of two headache days per month and the high omega 3 plus low omega 6 diet group saw a reduction of four headache days per month. Participants in the intervention groups also reported shorter and less severe headaches compared with those in the control group.

Although this is statistically a negative study with regard to the primary clinical endpoint, several factors make the overall findings clinically meaningful. International Headache Society guidelines and regulatory standards specify the use of headache or migraine frequency as the preferred outcome measure for trials of preventive interventions for migraine.[8] Interpretation of this study's findings is therefore complex: the study was negative according to the prespecified primary outcome, but would have been positive if judged by more guideline adherent endpoints. Also worth noting, the intervention groups experienced a clinically meaningful reduction in HIT-6 scores compared with baseline scores and compared with the control group (high omega 3: −1.5 *v* control; high omega 3 plus low omega 6: −1.6 *v* control).[9]

Ramsden and colleagues' results are also notable for the magnitude of the response to intervention. Clinical trials of recently approved pharmacological treatments for migraine prevention, such as monoclonal antibodies to the calcitonin gene related peptide, reported reductions of approximately 2–2.5 headache days per month in the intervention group compared with placebo.[10] The new trial suggests that a dietary intervention can be comparable or better.

These robust findings are even more remarkable because roughly two thirds of the study population met the criteria for chronic migraine (>15 headache days per month) and a little over half met the criteria for drug overuse headache, populations which are typically more refractory to

Endpoints at week 16 (intention-to-treat analysis)

	H3 (n=61) *v* control (n=60)			H3-L6 (n=61) *v* control (n=60)		
Endpoints	Difference (95% CI)	P value	Cohen's d	Difference (95% CI)	P value	Cohen's d
17-HDHA in plasma (log ng/mL)	0.7 (0.4 to 1.1)	<0.001	0.83	0.6 (0.2 to 0.9)	0.001	0.64
HIT-6 score	−1.5 (−4.2 to 1.2)	0.27	−0.21	−1.6 (−4.2 to 1.0)	0.23	−0.22
Headache hours per day	−1.3 (−2.1 to −0.5)	0.001	−0.56	−1.7 (−2.5 to −0.9)	<0.001	−0.71
Moderate to severe headache hours per day	−0.7 (−1.1 to −0.3)	<0.001	−0.58	−0.8 (−1.2 to −0.4)	<0.001	−0.62
Headache days per month	−2.0 (−3.3 to −0.7)	0.003	−0.55	−4.0 (−5.2 to −2.7)	<0.001	−1.13

17-HDHA=17-hydroxydocosahexaenoic acid; H3=increasing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA); H3-L6=increasing EPA and DHA, while reducing linoleic acid; HIT-6=six item headache impact test.

Funding, competing interests, and data sharing Funding from the National Institutes of Health (NIH). NIH claims intellectual property related to stable analogues of oxidised lipid mediators, with CER and GSK named as inventors. Data available on request.

Trial registration ClinicalTrials.gov NCT02012790.

treatment.[11 12] Finally, it is reassuring that the intervention diets increased 17-HDHA as expected, which supports the concept that there is a biological underpinning to the study findings.

These results support recommending a high omega 3 diet to patients in clinical practice. The major barrier to widespread success of any dietary intervention is adherence because strict diets require time, financial investment, and change in habits.[13 14] Therefore, it will be crucial for future research to determine how easy or difficult it is for patients to implement diets rich in omega 3 fatty acids at home, with or without lowering intake of omega 6. A clear template developed by nutritionists and patients would also be valuable to help people with migraine sustain these diets over longer periods.

Many people with migraine are highly motivated and interested in dietary changes, and clinicians might want to provide patients with information about the diets described in the study by Ramsden and colleagues. These authors manipulated dietary oils, butters, and proteins (such as fish) to achieve the required fatty acid composition. Their results take us one step closer to a goal long sought by headache patients and those who care for them: a migraine diet backed up by robust clinical trial results.

Cite this as: *BMJ* 2021;374:n1535

Find the full version with references at http://dx.doi.org/10.1136/bmj.n1535

Risk of hospital admission for patients with SARS-CoV-2 variant B.1.1.7

Nyberg T, Twohig KA, Harris RJ, et al

Cite this as: *BMJ* 2021;373:n1412
Find this at: http://dx.doi.org/10.1136/bmj.n1412

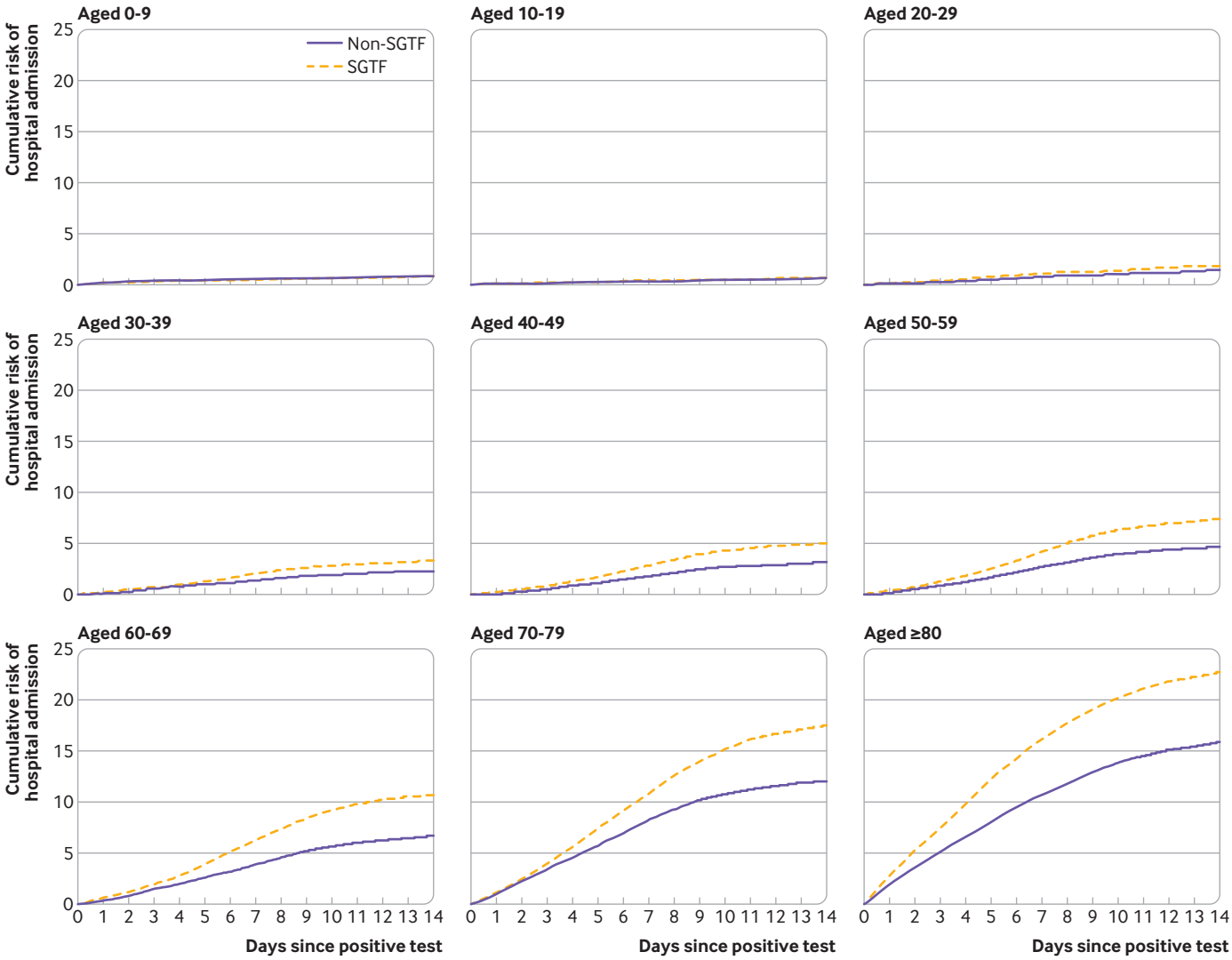
Study question Is community diagnosis of covid-19 with SARS-CoV-2 variant B.1.1.7 associated with a higher risk of hospital admission than diagnosis with wild type SARS-CoV-2 variants?

Methods A cohort of 839 278 patients with laboratory confirmed covid-19 tested in England between 23 November 2020 and 31 January 2021, for whom data on S gene target failure (SGTF), a proxy test for the B.1.1.7 variant, were available, were retrospectively followed up for hospital admission through individual linkage to hospital admission records. Adjusted hazard ratios of hospital admission within one to 14 days after a first positive test result were estimated by Cox regression with stratification for age, sex, ethnicity, deprivation, region of residence, and date of positive test result.

Study answer and limitations The adjusted hazard ratio of hospital admission within one to 14 days after the first positive test result for SARS-CoV-2 was 1.52 (95% confidence interval 1.47 to 1.57) for patients with SGTF compared with non-SGTF variants. The effect was modified by age (P<0.001), with hazard ratios of 0.93-1.21 in those younger than 20 years and 1.45-1.65 in age groups of 30 years and older. The adjusted absolute risk of hospital admission within 14 days was 4.7% (95% confidence interval 4.6% to 4.7%) for patients with SGTF variants and 3.5% (3.4% to 3.5%) for those without them. Limitations include the reliance on community testing data, which could include patients with covid-19 with less severe disease than those who present directly to emergency or other healthcare services.

What this study adds The risk of hospital admission was higher for patients infected with the B.1.1.7 variant compared with wild type SARS-CoV-2, likely reflecting a more severe disease. The higher severity might be specific to those older than 30 years.

Funding, competing interests, and data sharing
Funding was provided by the Medical Research Council and MRC UKRI/DHSC NIHR. No competing interests. The non-publicly available data used for this analysis may be requested from the Public Health England Office for Data Release.



Cumulative risk of hospital admission within 1-14 days after positive SARS-CoV-2 test result, by age group. Risks were estimated with Cox regression stratified by S gene target failure (SGTF) status and age group, adjusted for sex, index of multiple deprivation fifth, ethnicity, region of residence, and calendar week (potential confounders set to mean covariate levels)