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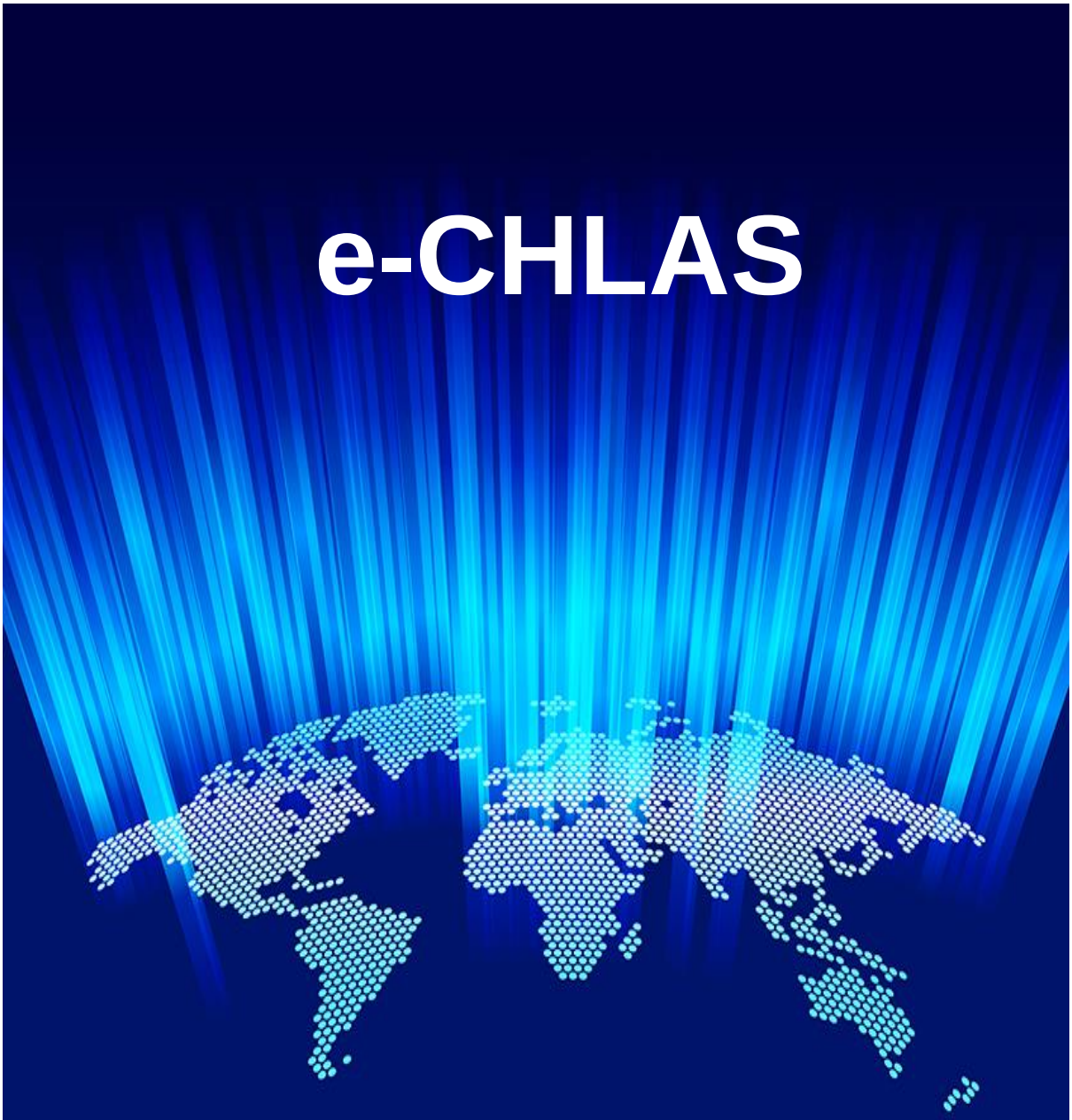

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PREFACE

Introduction

The library of the Central Council for Research in Homoeopathy has been circulating "Current Health Literature Awareness Service" (CHLAS). The main objective is to disseminate precise information/citation about scientific articles published in various journals/magazine subscribed by this Council.

Scope

This volume covers articles on AYUSH & other systems and Allied Sciences

Arrangement of Entries

The articles are indexed under the name of the authors, arranged in alphabetical order. The enteries have been made in the following order:

Author
Title
Name of Journal
year of publication; Volume (issue no.): pagination
Abstract

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We are grateful to Dr. Subhash Kaushik, Director General, CCRH for his encouragement and valuable suggestions from time to time. We sincere acknowledge the cooperation of Mrs. Nisha Adhikari, Office Assistant in compiling this bulletin.

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AYUSH & Other System

Akhavan Zanjani M, Rahmani S, Mehranfar S, Zarrin M, Bazyar H, Moradi Poodeh B et al. Soy Foods and the Risk of Fracture: A Systematic Review of Prospective Cohort Studies. *Complementary Medicine Research: 2022;* 29(2): 172-81p.

Abstract:

Objectives: The primary objective of our study was to systematically review all available prospective cohort studies which investigated the association of soy food intake and incident fracture risk.

Methods: We searched PubMed, Scopus, and Embase databases for relevant studies up to June 2021.

Synthesis: Of 695 records, a total of 5 cohort studies were included in the current systematic review. Two studies that were performed in China evaluated hip fracture while 2 studies that were done in Singapore evaluated any kind of fractures. The other study was conducted in Japan and evaluated osteoporosis fractures. All studies used a face-to-face interview to assess the dietary intake of soy foods. All 5 cohort studies were determined to be of high quality. One study considered soy food as a part of a vegetables-fruit-soy food dietary pattern. Others reported the association of dietary intake of soy foods with the risk of fractures.

Conclusion: The evidence from prospective cohort studies was suggestive for a protective role of soy foods, alone or within a dietary pattern, in the risk of incident fracture among Asian women, particularly for those in early menopause and those who used fermented soy products. But for men, the association was not significant. However, more cohort studies, including non-Asian populations, are required to confirm this association fully.

Ansariniaki Mehri, Behnam Behnaz, Keyghobady Seyfollah, Izadisabet Farideh, Soleimani Mohsen. Effects of aromatherapy with clove essential oil on memory function of patients during electroconvulsive therapy: A randomized controlled trial. *European Journal of Integrative Medicine: 2022;* 51: Article 102121

Abstract:

Introduction: Memory impairment is a common concern after receiving electroconvulsive therapy (ECT). The present study was conducted to investigate the effect of clove essential oil on memory improvement after electroconvulsive therapy (ECT).

Methods: For this randomized controlled trial, 100 patients undergoing ECT were assigned to either the experimental group, which was to receive clove essential oil 2.5% for 5 min three times a week, or the control group,

which was to receive routine care. The Wechsler Memory Scale-III (WMS-III) was used to evaluate memory in the patients before and after the first and second weeks of ECT. A blood cortisol test was also performed to measure their cortisol levels one and two weeks after the intervention.

Results: The patients' baseline memory score did not differ between the two groups (P = 0.67). The memory score increased in the first week after ECT, it decreased in the second week in both groups but after adjusting for time, no significant differences were observed in the total memory score between the two groups (P = 0.67). The pairwise comparison of the memory score between the first and second weeks also suggested insignificant differences in the experimental group and significant differences in the controls (P = 0.01). Although cortisol levels decreased significantly in both groups after ECT (P = 0.005), the difference between the two groups was insignificant both before (P = 0.40) and after (P = 0.26) ECT.

Conclusion: According to the present findings, clove essential oil neither improved memory in the patients nor affected their cortisol levels after ECT. Registered with the Iranian Registry of Clinical Trials (IRCT2014032317072N1).

Azad Afrooz, Pourtaheri Mohaddeseh, Darsareh Fatemeh, Heidari Solmaz, Mehrnoush Vahid. Evening primrose oil for cervical ripening prior to labor induction in post-term pregnancies: A randomized controlled trial. *European Journal of Integrative Medicine: 2022;* 51: Article 102123

Abstract:

Introduction: Cervical ripening can be induced using a variety of methods. It is used in cases where the cervix is in an unfavorable state prior to the start of the labor induction. The purpose of this study was to investigate how vaginal administration of evening primrose oil (EPO) affects cervical ripening in women who were scheduled for labor induction.

Methods: This randomized controlled trial was conducted from November 2018 to December 2019. The inclusion criteria were as follows: age 18-35 years old, first pregnancy, a live singleton baby with a cephalic presentation, gestational age≥ 41 weeks, intact membranes, normal cardiotocography, and a Bishop score of ≤ 4. Two hundred women were randomly assigned to a single vaginal dose of 1000 mg evening primrose oil (n=100) or placebo (n=100). Any change in Bishop score was considered the primary outcome variable in the efficacy evaluation.

Results: Of 200 eligible women, 25 women were excluded for various reasons. Finally, statistical analysis was performed on 175 women (88 women in the experimental group and 87 in the control group). At baseline there was no significant difference between the two groups in Bishop score. However, after the intervention, this score was significantly higher in the experimental group than in the control group (Mean Difference: 3.29, 95%

Confidence Interval: 3.51 to 1.18). No adverse effects were observed or reported.

Conclusions: Vaginal application of EPO at a single dose of 1000 mg at 41 weeks gestation improved Bishop score and reduced parturition time in post-term pregnancies.

Baltacı N, Başer M. Effect of Lullaby Intervention on Anxiety and Prenatal Attachment in Women with High-Risk Pregnancy: A Randomized Controlled Study. *Complementary Medicine Research: 2022;* 29(2): 127-35p.

Abstract:

Background: Women with high-risk pregnancy experience anxiety and low mother-fetal attachment when faced with signs of danger and health problems. This study aimed to investigate the effects of lullaby intervention on anxiety and prenatal attachment in women with high-risk pregnancy.

Materials and Methods: This randomized controlled trial was conducted in the perinatology clinic of a state maternity hospital in Turkey. Seventy-six women with high-risk pregnancy were included. The intervention group listened to lullabies for 20 min once a day, and accompanied by lullabies touched their abdomen and thought about their babies, but the control group did not. Data were collected using the Pregnant Information Form, the State Anxiety Inventory, and the Prenatal Attachment Inventory.

Results: Baseline anxiety did not differ in the intervention versus control group (47.83 ± 10.74 vs. 44.10 ± 8.08, mean difference 3.73 [95% Cl –1.18 to 8.64], $p = 0.13$), but after the 2nd day lullaby intervention anxiety was lower in the intervention group versus control group (33.66 ± 9.32 vs. 43.06 ± 8.10, mean difference –9.40 [95% Cl –13.91 to –4.88], $p < 0.01$). Baseline prenatal attachment did not differ in the intervention versus control group (56.03 ± 10.71 vs. 53.86 ± 9.98, mean difference 2.16 [95% Cl –3.18 to 7.51], $p = 0.42$), but after the 2nd day lullaby intervention prenatal attachment was higher in the intervention group versus control group (66.70 ± 7.60 vs. 54.36 ± 9.52, mean difference 12.33 [95% Cl 7.87 to 16.78], $p < 0.01$). In the within-group analysis the intervention group had lower anxiety and better prenatal attachment ($p < 0.01$), but not in the control group ($p > 0.05$).

Conclusion: Lullaby intervention can play an effective role in reducing anxiety and improving prenatal attachment. The use of this integrative, noninvasive, non-pharmacologic, time-efficient, and natural intervention is suggested in the care of pregnant women.

Bartlik Barbara, Mindes Janet. Clinician Wellness Self-Care for Staying Healthy: Attention to Sexual Life. *Integrative and Complementary Therapies: 2022;* 28(2): 72-74p.

Bonjour Matthieu, Gabriel Sahmla, Valencia Analila, Goldhamer Alan C, Myers Toshia R. Challenging Case in Clinical Practice: Prolonged Water-Only Fasting Followed by an Exclusively Whole-Plant-Food Diet in the Management of Severe Plaque Psoriasis. *Integrative and Complementary Therapies: 2022;* 28(2): 85-87p.

Cramer Holger. Social Prescribing: Bringing the Community (Back) into Medicine. *Journal of Integrative and Complementary Medicine: 2022;* 28(4): 285-86p.

Dabrh Abd Moain Abu, Meore Anne, Wilson Edward W, Perlman Adam. Horticultural Therapy: An Ancient Integrative Approach for Modern Times. *Journal of Integrative and Complementary Medicine: 2022;* 28(4): 290-93p.

Ghazanfari MJ, Karkhah S, Emami Zeydi A, Mortazavi H, Tabatabaee A, Adib Hajbaghery M. Systematic Review of Potentially Effective Nonpharmacological Interventions for Reducing Fatigue among Iranian Patients Who Receive Hemodialysis. *Complementary Medicine Research: 2022;* 29(2): 147-57p.

Abstract:

Background and Purpose: Fatigue control in hemodialysis (HD) patients requires a multidisciplinary approach. This study aimed to comprehensively review the available research literature regarding the nonpharmacological interventions used for reducing fatigue among Iranian HD patients.

Methods: In this systematic review, an extensive search of the literature was conducted on PubMed, Web of Science, and Scopus databases, using the keywords related to the purpose. Also, the Persian equivalent of these keywords was searched in Iranian databases, such as Iranmedex and Scientific Information Database (SID) from the inception to June 16, 2020.

Results: Of 2,761 articles, 25 studies were included in the review. Among a total of 1,748 Iranian HD patients with a mean age of 54.17 (SD = 12.27) years, 61.38% were male. Interventions such as educational-based programs (n = 5), nutrition-based programs (n = 2), massage therapy (n = 3), exercise-based programs (n = 4), relaxation technique (n = 3), combination of relaxation technique and inhalation aromatherapy (n = 1), energy therapy (reflexology and acupressure) (n = 3), and mind-guided imagery (n = 1) were effective in reducing fatigue in Iranian HD patients.

Discussion/Conclusion: These simple, low-cost, and practical interventions can be used for the reduction of fatigue among HD patients by nurses. However, future well-designed studies are recommended to confirm the efficacy of these and other potentially effective interventions for reducing fatigue in HD patients.

Gilbert Isabelle, Gaudreault Nathaly, Gaboury Isabelle. Exploring the Effects of Standardized Soft Tissue Mobilization on the Viscoelastic Properties, Pressure Pain Thresholds, and Tactile Pressure Thresholds of the Cesarean Section Scar. *Journal of Integrative and Complementary Medicine: 2022;* 28(4): 355-62p.

Abstract:

Background: Objectives of soft tissue mobilization applied to cesarean section (C-section) scars are to decrease stiffness and to reduce pain. Research investigating these effects is lacking.

Materials and methods: The authors conducted a descriptive, exploratory, proof-of-concept clinical study. Women aged 18 to 40 years who had undergone at least one C-section were recruited. A trained osteopath performed standardized mobilization of the C-section scar once a week for 2 weeks. Scar quality and pain characteristics, viscoelastic properties, pressure pain thresholds, and tactile pressure thresholds were measured before and after each session. Paired Student's t-tests and Friedman's test with Dunn–Bonferroni adjustment were performed to assess the immediate and short-term effects of mobilizations. Kendall's W and Cohen's d were calculated to determine effect sizes over the short term. Simple bootstrapped bias-corrected and accelerated 95% median confidence intervals were computed.

Results: Thirty-two participants completed the study. The Patient and Observer Scar Assessment Scale questionnaire revealed differences with small and moderate effects for stiffness ($p = 0.021$, $d = 0.43$), relief ($p < 0.001$, $d = 0.28$), surface area ($p = 0.040$, $d = 0.36$), flexibility ($p = 0.007$, $d = 0.52$), and participant opinion ($p = 0.001$, $d = 0.62$). Mobilizations increased elasticity ($p < 0.001$, $W = 0.11$), decreased stiffness ($p < 0.001$, $W = 0.30$), and improved pressure pain thresholds ($p < 0.001$, $W = 0.10$) of the C-section, with small to moderate effects. The results also showed decreased tone and mechanical stress relaxation time, as well as increased tactile pressure thresholds at the different measurement times ($p < 0.05$), but trivial effect sizes ($W < 0.10$). Creep showed trivial effect and no significant difference ($p = 0.09$).

Conclusion: This study showed that two sessions of mobilization of C-section scar might have a beneficial effect on some viscoelastic properties of the C-section as well as on pain. Some variables of interest useful for future empirical studies are highlighted.

Guerin Christilynn, Attli Bisleen, Cooley Kieran, Hassan Samah, Sarebanha Shadi, Sadrolsadot Paymon et al. Assessment of Naturopathic Treatments, Health Concerns, and Common Comorbid Conditions in Fibromyalgia Patients: A Retrospective Medical Record Review. *Journal of Integrative and Complementary Medicine: 2022;* 28(4): 363-72p.

Abstract:

Background: Fibromyalgia (FM) is characterized by chronic pain, with allodynia and hyperalgesia being the most common signs. Many patients with FM explore, express interest, and use complementary and alternative medicine to help manage symptoms and improve quality of life. However, little is known about the clinical recommendations provided by naturopathic doctors (NDs).

Objective: To describe trends in assessment and treatment of patients with FM by NDs.

Methods: Retrospectively, medical records of 200 patients with the FM ICD-10 code were reviewed from the Robert Schad Naturopathic Clinic. Of these records, 70 met inclusion criteria and were further analyzed. Comorbid conditions, health concerns, physical and psychological examinations, and treatment were recorded. Patients were excluded if informed consent for research was not signed. The project was approved by the Research Ethics Board of the Canadian College of Naturopathic Medicine.

Results: Seventy patients met criteria and were included in the current analysis. Most patients identified as female (96%). Vitamin D (57%), magnesium (54%), omega-3 fish oil (53%), acupuncture by an acupuncturist (53%) or an ND (40%), B12 orally or by injection (40%), and probiotics (40%) were highly utilized treatments. A past/current medical history of digestive complaints (64%) and depression/mental illness (63%) were common comorbidities, alongside a history of arthritic conditions (53%) and anxiety (43%). A family history of arthritic conditions (47%) was also prevalent. The Widespread Pain Index and Symptom Severity tool (43%) was used to assess pain and other symptoms. No adverse effects of treatment were readily identifiable.

Conclusion: Findings from this study reveal elements of both consistency and variability in the treatment recommendations from NDs in a teaching clinic environment. Future research that assesses or compares treatment recommendations for FM in other settings may be informative to better understand health services, the nature of individualized care, and patient experiences.

Harbell Monica W, Barendrick Lindsay N, Mi Lanyu, Quillen Jaxon, Millstine Denise M. Patient Attitudes Toward Acupuncture in the Perioperative Setting. *Journal of Integrative and Complementary Medicine: 2022;* 28(4): 349-54p.

Abstract:

Introduction: Acupuncture is a potential treatment option for pain, nausea, vomiting, anxiety, and agitation in the perioperative period. Patient preference for participating in acupuncture in the perioperative period is

not well understood. The aim of this study was to quantify patient interest in perioperative acupuncture, explore the relationship between acupuncture interest, insurance coverage and patient cost, and identify clinical factors associated with patient interest in acupuncture.

Materials and Methods: Adult patients evaluated in the Preoperative Evaluation Clinic at the Mayo Clinic in Phoenix, AZ, between June 2019 and July 2019, received a voluntary survey to assess their attitudes toward receiving acupuncture in the perioperative period. Patient interest in acupuncture to help treat pain, anxiety, and postoperative nausea and vomiting, as well as their willingness to pay for such services, were assessed. Demographic data, American Society of Anesthesiologists (ASA) physical class, scheduled procedure, and insurance coverage were extracted from the medical record. Univariate analysis was performed to estimate interest in acupuncture.

Results: Three hundred and seven respondents were included in this study with a response rate of 60.4%. A total of 68.4% of study participants were interested in receiving perioperative acupuncture. Of those interested in acupuncture, 86.7% were interested if acupuncture was offered at no cost (either free or fully covered by insurance). A total of 47.1% of those patients interested in acupuncture would be interested if the cost of acupuncture was between 20 and 50 U.S. dollars. A total of 8.6% would be interested in acupuncture if patients were expected to pay the full cost of treatment (estimated 175 U.S. dollars). Age, sex, ASA status, type of surgery, risk of procedure, and Medicare/Medicaid coverage were not statistically associated with interest in acupuncture.

Conclusions: When there is little to no direct cost to the patient, the majority of patients are interested in acupuncture in the perioperative period.

Hart Jane. Chromotherapy: Color and Light Therapies May Benefit Health. *Integrative and Complementary Therapies: 2022;* 28(2): 104-06p.

Hopkins Sarah W, Greenberg Jonathan, Isaacs Jordan, Vranceanu Ana-Maria. Practice Makes Perfect? Associations Between Home Practice and Physical and Emotional Function Outcomes Among Patients with Chronic Pain Enrolled in a Mind–Body Program. *Journal of Integrative and Complementary Medicine: 2022;* 28(4): 320-27p.

Abstract:

Objectives: To summarize the characteristics of home practice adherence in patients with chronic pain randomized to a 10-week group mind–body activity program with (GetActive-Fitbit) and without (GetActive) a digital monitoring device, and test the association between home practice adherence and improvement in physical and emotional treatment outcomes.

Methods: Data were collected in a pilot randomized controlled trial (RCT) of the GetActive (n = 41) and GetActive-Fitbit (n = 41) programs. Participants submitted weekly home practice logs depicting their daily physical activity and practice of relaxation and gratitude skills. Participants completed assessments of physical (patient-reported, performance-based, and accelerometer-measured) and emotional function outcomes both before and after the programs. Participants in both programs were combined due to the identical session and home practice content.

Results: Participants reported engaging in physical activity on average 30.62 days (SD = 20.28, 48.6% of intervention days), relaxation skill practice on average 29.87 days (SD = 21.16, 47.4% of intervention days), and gratitude practice on average 32.10 days (SD = 22.12, 51.0% of intervention days). The average duration of physical activity and relaxation skill practice were 44.40 min a day (SD = 59.44) and 11.15 min a day (SD = 12.00), respectively. The duration of physical activity was significantly associated with decrease depression symptoms ($p = 0.049$, $\eta^2 = 0.056$). No other association was found between home practice and change in outcomes.

Conclusions: Patients with chronic pain are generally able and willing to engage in home practice during a mind–body activity intervention. Emphasizing longer duration of physical activity practice may contribute to an improvement in depression. Future fully powered RCTs with rigorous assessment of home practice adherence and dose-response designs may further elucidate the role of home practice in improvements in treatment outcomes.

Jia Dongming, Zhou Jiaxin, Xu Yuming. Effectiveness of Traditional Chinese Health-Promoting Exercise as an Adjunct Therapy for Drug Use Disorders: A Systematic Review and Meta-Analysis. *Journal of Integrative and Complementary Medicine: 2022;* 28(4): 294-308p.

Abstract:

Objective: Meta-analysis was used to quantitatively examine the effectiveness of Traditional Chinese Health-Promoting Exercise (TCE) as an adjuvant therapy for drug use disorders and rehabilitation based on previously published studies.

Methods: Potential literature was retrieved by searching eight electronic databases (China National Knowledge Infrastructure [CNKI], Wanfang, Chinese Scientific Journal Database, China Biology Medicine [CBM],

PubMed, Embase, Cochrane Library, and EBSCOhost) from January 2000 to May 2021, as well as through manual searches, including email. These literature reports comprised randomized, controlled trial studies and nonrandomized, controlled trial studies assessing the effects of TCE intervention on the physical and psychological (mental) health of drug addicts. The quality and bias risk of each study were assessed using the Cochrane bias risk assessment tool. The RevMan5.3 statistical software was employed to evaluate the methodological quality of the included studies, and sensitivity and subgroup analyses using the Stata16.0 MP software were performed to explore the sources of heterogeneity among the data. This study is registered on PROSPERO (CRD42021254124).

Results: Data from 14 studies (1094 individuals with drug abuse) meeting the inclusion criteria were extracted for meta-analysis. Compared to the control group, TCE intervention induced significant improvements in the systolic blood pressure (standardized mean difference [SMD] = −0.42, $p < 0.05$), diastolic blood pressure (SMD = −0.34, $p < 0.05$), one-leg stand with eyes closed (SMD = 0.74, $p < 0.05$), Symptom Check List (SMD = −0.42, $p < 0.05$), anxiety scale (self-rating anxiety scale/STI) (SMD = −0.49, $p < 0.05$), and depression scale (self-rating depression scale/Beck Depression Inventory/Hamilton Depression Rating Scale for Depression) (SMD = −0.37, $p < 0.05$). Sensitivity and subgroup analyses of the individual outcome indicators with high heterogeneity ($I2 \geq 50\%$, $p < 0.10$) were performed to further explore the source of heterogeneity. The results of the sensitivity analysis showed that, after removing studies one by one, the heterogeneity of the data remained high ($I2 > 50$), and the difference of synthetic overall effect did not change ($p < 0.05$), indicating that the sensitivity was low and that the results were robust and reliable. The results of the subgroup analysis results indicated that the gender of the participants and the drug type were the sources of heterogeneity.

Conclusion: As an effective mind-body movement intervention, long-term TCE is beneficial to improving the physical and mental health of drug addicts. The specific intervention methods are dependent on the gender of the addict and the drug type, and longer intervention times yielded greater impacts on their physical health.

Jyung Hyowoun, Mah Donna M, Moonaz Steffany, Rai Manisha, Bhandiwad Anup, Nielsen Arya et al. Pain Left, I Was Off and Running": A Qualitative Analysis of Group Acupuncture and Yoga Therapy for Chronic Pain in a Low-Income and Ethnically Diverse Population. ***Journal of Integrative and Complementary Medicine: 2022;*** **28(4): 328-38p.**

Abstract:

Introduction: Chronic pain and the current opioid epidemic are pressing public health concerns, especially in low-income and ethnically diverse communities. Nonpharmacologic therapies that are safe, effective, and acceptable for the treatment of chronic pain conditions may provide a

solution for addressing this issue. This qualitative analysis explores the experience of study participants who received combined acupuncture and yoga therapy (YT) to treat chronic pain delivered in a primary care setting.

Methods: The group acupuncture with yoga therapy for chronic neck, low back, and osteoarthritic pain trial (GAPYOGA) assessed the feasibility and effectiveness of group acupuncture (GA) combined with YT in a low-income, racial, and ethnically diverse population. Individual in-depth interviews were conducted with a subset of patients in the trial. Nineteen participants were interviewed for qualitative analysis of their experience. Using the immersion and crystallization method, transcribed interviews were analyzed for themes meaningfully representing participant experience.

Results: The combined GA and YT resulted in significant pain relief and transformative healing experiences. Three themes emerged from participant narratives: (1) transformative engagement with self in the healing process through pain relief, psychological well-being, and self-efficacy; (2) therapeutic relationship with acupuncture and yoga providers; and (3) fostering relationships with fellow participants in the group.

Discussion: In this study of a low-income and ethnically diverse population, the combination of acupuncture and YT was found to alleviate pain, improve function, promote psychological well-being, and engage participants in self-care practices in a transformative healing process—resulting in physical and psychological benefits.

Korn Leslie, Rountree Robert. Nutritional Psychology and Somatic Approaches for Optimal Health: A Clinical Conversation. ***Integrative and Complementary Therapies: 2022;*** **28(2): 53-61p.**

Lucius Khara. Migraine Headache: Dietary Approaches and Nutritional Supplements. ***Integrative and Complementary Therapies: 2022;*** **28(2): 93-103p.**

Abstract:

Migraine headaches are a common concern, significantly impacting quality of life for the sufferer, as well as work and social function. For many people that experience migraines, the response to pharmacologic management may be incomplete. Because of this, there is a strong need for additional supportive strategies in these individuals. Removal of individual dietary triggers is a useful strategy for many people with migraines. Nutritional supplements and botanical medicines (or phytonutrients) that may be considered include magnesium, riboflavin, alpha lipoic acid, coenzyme Q10, feverfew, curcumin, and butterbur.

Mai Qiulu, Li Xuejing, Yang Dan, Zhang Xiaoyan, Hao Yufang. Effects of acupressure on cancer-related pain management: A systematic review and meta-analysis of randomized controlled trials. ***European Journal of Integrative Medicine: 2022;*** **51: Article 102120**

Abstract:

Introduction: Acupressure is a non-invasive complementary treatment method that can positively affect the relief of cancer pain symptoms. The results from clinical trials have revealed that the effects of acupressure (including auricular acupressure) on cancer pain management are inconsistent. Our objective was to systematically evaluate the effect of acupressure on cancer pain.

Methods: Seven databases (CNKI, VIP, Wanfang Database, SinoMed, Pubmed, Embase, and The Cochrane Library) were searched from their inception to November 2021 for randomized controlled trials (RCTs) of acupressure used for cancer pain. All analyses were conducted by RevMan5.3. The Cochrane RoB tool and GRADE were used to assess the risk bias and quality of evidence, respectively.

Results: Twenty-eight RCTs involving 2630 patients were included. Combined results showed the acupressure group had better outcomes in pain remission rate [RR 1.20, 95%CI (1.10, 1.30), P < 0.0001, I^2= 61%], pain intensity [SMD -1.78, 95% CI, (-2.21, -1.35), P < 0.00001, I2= 94%], quality of life [SMD 0.62, 95%CI (0.35, 0.89), P<0.00001, I2=61%], patient satisfaction with analgesia [RR 1.14, 95%CI (1.05, 1.23), P = 0.001, I2=43%] compared with a control group. Two studies mentioned that acupressure as an adjunctive treatment could reduce the dose of analgesics. The bias of most studies was unclear because of irregular reporting according to the ROB tool, and meanwhile, most studies had high risk with no blinding. The GRADE evidence level was rated as moderate to very low. No studies measured adverse reactions.

Conclusion: Acupressure (including auricular acupressure) group seemed to be more effective than the control group for cancer pain. However, the results were inconclusive due to weak evidence, and robust methodological RCTs with appropriate blinding are still needed to reconfirm the findings of our review.

Miralizadeh Aysan, Peyman Akram, Soltani Neda Jamali, Ashktorab Tahereh. Comparison of the Effect of Foot and Palm Reflexology Massage on Respiratory Distress Syndrome in Premature Infants under Noninvasive Ventilation. *Complementary Medicine Research: 2022;* 29(2): 100-108p.

Abstract:

Introduction: Respiratory distress is one of the life-threatening conditions in preterm infants. Sensory deprivation in preterm infants hospitalized in the intensive care units affects their physiological and psychological development. Therefore, this study is an attempt to compare the effects of foot and palm reflexology on respiratory distress in infants subjected to noninvasive ventilation.

Methods: In this clinical study, 150 infants hospitalized at Fatemieh Hospital in Hamadan were randomly assigned to 3 groups. In the intervention groups, the reflexology massage to foot and palm was performed for 10 min within 3 days in 6 rounds. In the control group, leg warming was performed. In each group, the personal information checklist, the respiratory distress score, oxygen saturation percentage, and respiratory rate before and after the daily intervention were examined. Data analysis was performed using the standard statistical tests in SPSS.

Results: The results mirrored the statistically significant difference between the intervention and control groups 3 days into the intervention with regard to the average oxygen saturation percentage, respiratory rate, and the respiratory distress score ($p < 0.05$). When eliminating the effect of confounding variables, therapeutic intervention applied to palm compared to foot had a greater effect on reducing respiratory distress score in the studied infants.

Conclusion: The reflexology massage method, especially palm reflexology massage, contributes to the mitigation of respiratory distress in preterm infants subjected to noninvasive ventilation. Hence, this low-cost and efficient intervention program can be recommended as a complementary method for preterm infants with respiratory distress.

Moderator: Hart Jane, Participants: Frates Beth, Vago David, Mehta Darshan. Meditation Roundtable Discussion: Cultivating Calm, Connection and Stress Relief in Difficult Times. ***Integrative and Complementary Therapies: 2022;*** **28(2): 65-71p.**

Ozturk Fatma Gokçenur, Sencan Irfan, Ozkara Adem, Yapar Aliekber, Ozturk Recep. Knowledge and experiences of complementary and alternative medical practices among patients presenting to an orthopedic clinic: A cross-sectional study. ***European Journal of Integrative Medicine: 2022;*** **51: Article 102117**

Petitpierre M, Stenz L, Paoloni Giacobino A. Epigenomic Changes after Acupuncture Treatment in Patients Suffering from Burnout. Complementary Medicine Research: 2022; 29(2): 109-19p.

Abstract:

Introduction: The effects of acupuncture treatment in patients suffering from burnout may imply an epigenetic control mediated by DNA methylation changes. In this observational study, a genome-wide characterization of epigenetic changes in blood DNA, before and after acupuncture treatment, was performed in a cohort of 11 patients suffering from burnout.

Methods: Burnout was assessed using the Maslach Burnout Inventory (MBI) and DNA was extracted from blood samples and analyzed by Illumina EPIC BeadChip.

Results: Before acupuncture, all patients suffered of emotional exhaustion (EE) (MBI-EE score, 44 ± 6), 81% suffered of depersonalization (DP) (MBI-DP score, 16 ± 6), and 72% of low feelings of personal accomplishment (PA) (MBI-PA score, 29 ± 9). After acupuncture, all MBI dimensions improved significantly (EE, 16 ± 11 [$p = 1.5 \times 10^{-4}$]; DP, 4 ± 5 [$p = 5.3 \times 10^{-4}$]; and PA, 40 ± 6 [$p = 4.1 \times 10^{-3}$]). For each patient, both methylomes obtained before and after acupuncture co-clustered in the multidimensional scaling plot, indicating a high level of similarity. Genes corresponding to the 10 most differentially methylated CpGs showed enrichment in the brain dopaminergic signaling, steroid synthesis and in the insulin sensitivity pathways.

Conclusion: Acupuncture treatment was found to be highly effective on all burnout dimensions and the epigenetic targets identified were involved in some major disturbances of this syndrome.

Ring Melinda. Culinary Medicine: Teaching Patients and Healthcare Students How to Impact Health Through Improved Nutrition and Cooking Skills. *Integrative and Complementary Therapies: 2022;* 28(2): 62-64p.

Saumaa Hiie. Improving Posture and Alignment Through Somatics. *Integrative and Complementary Therapies: 2022;* 28(2): 88-92p.

Selfe Terry Kit, Montgomery Caitlin, Klatt Maryanna, Wen Sijin, Sherman Karen J, Innes Kim E. Exploratory Randomized Controlled Trial of a 12-Week Yoga Versus Educational Film Program for the Management of Restless Legs Syndrome: Feasibility and Acceptability. *Journal of Integrative and Complementary Medicine: 2022;* 28(4): 309-19p.

Abstract:

Objectives: The primary objectives of this pilot trial were to assess the study feasibility and acceptability of the 12-week yoga and educational film programs for the management of restless legs syndrome (RLS) in preparation for a future randomized controlled trial (RCT).

Materials and Methods: This pilot, parallel-arm, randomized feasibility trial was conducted at two sites, Morgantown, WV and Columbus, OH. Yoga group participants attended 75-min Iyengar yoga classes, twice weekly for 4 weeks, then once a week for 8 weeks (16 total classes), and completed a 30-min homework routine on nonclass days. Educational film group participants attended once weekly, 75-min classes (12 total classes), which included information on RLS and other sleep disorders, RLS management including sleep hygiene practices, and complementary therapies. Feasibility and acceptability outcomes included program satisfaction and recruitment, retention, and adherence rates. In addition, participants were asked their preferences regarding three yoga class schedule scenarios for a future

study. Attendance, yoga, and treatment logs were collected weekly. Program evaluation and yoga scheduling questionnaires were collected at week 12.

Results: Forty-one adults with moderate to severe RLS were randomized to a 12-week yoga (n = 19) or educational film (n = 22) program. Thirty participants (73%) completed the program. Yoga and education group participants attended an average of 13.0 ± 0.84 (81%) and 10.3 ± 0.3 classes (85%), respectively. Participants from both groups indicated satisfaction with the study. All yoga group respondents to the program evaluation reported they would likely (n = 6) or very likely (n = 7) continue yoga practice; 86.7% of education group respondents (13 of 15) indicated that they were likely (n = 7) or very likely (n = 6) to make lasting changes based on what they had learned. The preferred schedule for a future study was a 16-week study with once-weekly yoga classes.

Conclusions: The findings of this study suggest that a larger RCT comparing yoga with an educational film group for the management of RLS is feasible.

Shang PP, Chen CT, Cheng M, Shi YL, Yang YQ, Wang Y. Analysis of Acupoint Selection and Combinations in Acupuncture Treatment of Asthma Based on Data Mining. *Complementary Medicine Research: 2022;* 29(2): 136-46p.

Abstract:

Objective: Asthma is a highly prevalent respiratory disease that remains difficult to control. Acupuncture, as an important alternative therapeutic modality in preventing and treating asthma, is widely used in the world due to its promising efficacy and safety. Although acupoint selection and combinations are critical to therapeutic effects of acupuncture, its fundamental rules for asthma have not been fully understood. Thus, using data mining, the present study aimed to discover the most effective acupoints and combinations in the acupuncture treatment of asthma.

Methods: Controlled clinical trials (CCTs) of acupuncture treatment for asthma were searched and retrieved from databases including Chinese National Knowledge Infrastructure (CNKI), Wanfang, and PubMed. Data regarding the main acupoints prescribed in these clinical trials was collected and quantified. A network analysis was performed to uncover the interconnections between the acupoints. Additionally, hierarchical clustering analysis and association rule mining were conducted to discover the potential acupoint combinations.

Results: A total of 183 CCTs were retrieved. Feishu (BL13), Dingchuan (EX-B1), Dazhui (GV14), Shengshu (BL23), Pishu (BL20), and Fengmen (BL12) appeared to be the most frequently used acupoints for asthma. While the Bladder Meridian of Foot Taiyang, the Governor Vessel, and the Conception Vessel, compared to other meridians, were found to be the more commonly selected meridians. In the acupoint interconnection

network, Feishu (BL13), Fengmen (BL12), Dingchuan (EX-B1), and Dazhui (GV14) were defined as key node acupoints. Moreover, acupoint clustering analysis revealed the treatment principle of "facilitating the flow of the lung Qi, tonifying spleen and kidney, and treating both the symptoms and root causes." Association rule mining analysis demonstrated that the combination of Pishu, Shenshu, Feishu, and Dingchuan, as well as that of Feishu, Dazhui, and Fengmen were potential acupoint combinations that should be selected with priority in asthma treatment.

Conclusion: Based on a data mining analysis of published CCTs, this study provides valuable information regarding the selection of the most effective acupoints and combinations for clinical acupuncture practice and experimental study aimed at the prevention and treatment of asthma.

Sharma SK, Kala N, Telles S. Volitional Yoga Breathing Influences Attention and Anxiety: An Exploratory Randomized Crossover Study. ***Complementary Medicine Research: 2022;*** **29(2): 120-26p.**

Abstract:

Background: Previous studies assessed yoga breathing practices individually. This exploratory, randomized crossover study assessed attention and anxiety following four yoga breathing practices, breath awareness, and quiet seated rest.

Materials and Methods: Thirty-eight male volunteers between 20 and 37 years (group mean age ± SD; 24.08 ± 4.01 years) were assessed in six sessions in random order (www.randomizer.org) on separate days. The sessions were: (i) alternate nostril yoga breathing, (ii) bellows yoga breathing, (iii) bumblebee yoga breathing, (iv) high-frequency yoga breathing, (v) breath awareness, and (vi) quiet seated rest. The sessions were for 18 min each. Six letter cancellation test (SLCT) and Spielberger's State Trait Anxiety Inventory-state (STAI-s) were administered pre and post each session. Data analysis used general linear mixed model analysis, with fixed effect of states (pre and post) and sessions.

Results: A significant main effect of states was observed on total attempted ($F_{1,407} = 5.374$, $p = 0.021$) and net attempted scores ($F_{1,407} = 6.178$, $p = 0.013$) of the SLCT, with a significant increase in scores following high-frequency yoga breathing (padj = 0.031 for total attempted scores; padj = 0.029 for net attempted scores). Also, a significant main effect of states on STAI-s scores was observed ($F_{1,407} = 33.979$, $p < 0.001$), with a significant decrease in scores following alternate nostril yoga breathing (padj = 0.001), bellows yoga breathing (padj = 0.008), bumblebee yoga breathing (padj = 0.002), and high-frequency yoga breathing (padj = 0.042) compared to the corresponding pre state. There was a significant main effect of sessions ($F_{5,407} = 3.043$, $p = 0.010$) on STAI-s scores, with scores post alternate nostril yoga breathing significantly lower than post breath awareness (padj = 0.037).

Conclusion: Following high-frequency yoga breathing sustained attention was better than before while state anxiety decreased in post-pre comparisons of alternate nostril yoga breathing, bellows yoga breathing, bumblebee yoga breathing, and high-frequency yoga breathing. The differences between breathing practices may be due to differences in degree of volitional regulation of breathing and in the breath patterns modified volitionally. The generalizability of the findings was limited by including an all male, yoga experienced sample. Future research should include participants of both genders and could include different levels of yoga experience, with assessments including objective measures of attention and anxiety.

Sylvain Berney, Barbara Broers, Jean Michel Gaspoz, Thierry Favrod Coune. Complementary and alternative medicines in patients with alcohol or tobacco use disorder: Use, expectations and beliefs. ***European Journal of Integrative Medicine: 2022;*** **51: Article 102115**

Weeks John. Insurance Commissioner Deborah Senn (1949–2022): A Personal Memoriam on Her Role in an Origin Story for the Integrative Era. ***Journal of Integrative and Complementary Medicine: 2022;*** **28(4): 287-89p.**

Yuchi Wu, Lihong Yang, Zhicong Zhong, Xiuqing Wu, Zhiren He, Hongyan Ma et al. Auricular Acupressure for Hemodialysis Patients with Insomnia: A Multicenter Double-Blind Randomized Sham-Controlled Trial. ***Journal of Integrative and Complementary Medicine: 2022;*** **28(4): 339-48p.**

Abstract:

Background and objectives: The effect of auricular acupressure (AA) for maintenance hemodialysis (MHD) patients with insomnia has been controversial. This study assessed the efficacy and safety of AA for MHD patients with chronic insomnia.

Design, setting, participants, and measurements: This was a multicenter, double-blind (participant and assessor), randomized sham-controlled trial. A total of 133 subjects were randomized to receive AA on active points (AA group, $n = 64$) or on sham auricular acupressure (SAA) points (SAA group, $n = 69$) for 8 weeks and followed up for 12 weeks. AA was provided by assigned qualified nurses who were not involved in assessment. The primary outcome was the clinical response rate, which was defined as the percentage of participants who reached a reduction of Pittsburgh Sleep Quality Index (PSQI) global score ≥3 in each group. Secondary outcomes included changes in PSQI scores over time, PSQI scores and hypnotics use at each visit, and changes in the weekly dose of hypnotics for drug-dependent subjects.

Results: At week 8, the AA group yielded a higher clinical response rate than the SAA group (AA: 55% vs. SAA: 36%, odds ratio: 1.5, 95% confidence interval: 1.0–2.2, $p = 0.033$). Both groups showed a reduction in PSQI global scores during treatment and follow-up, compared with the baseline, respectively. A significant change of PSQI global score was observed over time ($F = 28.387$, $p < 0.001$). PSQI global score of the AA group was relatively lower than that of the SAA group at each visit ($p < 0.05$ at week 16 and 20). For those depending on hypnotics, AA reduced their consumption of hypnotics. The intervention was safe, and its adherence was satisfactory.

Conclusion: AA could serve as a complementary or alternative therapy for MHD patients with insomnia by improving their sleep quality and reducing their use of hypnotics.

Zarco Emilia Patricia T, Aquino Michele, Petrizzo John, Wygand John, King Jessica. Impact of a 10-Week Essentrics Program on Strength, Flexibility and Body Composition. ***Integrative and Complementary Therapies: 2022;*** **28(2): 75-84p.**

Abstract:

Background: Essentrics is a dynamic exercise program that uses a combination of calisthenics and flexibility training, sharing similarities with Tai Chi, Yoga and Pilates.

Methods: An experimental study assessed the effect of a 10-week Essentrics exercise program on muscular strength, flexibility and body composition. Twelve undergraduate students performed supervised Essentrics exercise twice weekly for 10 weeks and underwent a battery of pre- and post-intervention tests consisting of chest press and leg press for muscular strength, standardized Young Men's Christian Association sit and reach test and the Shoulder Mobility Test of the Functional Movement Screen for flexibility and dual energy X-ray absorptiometry for body composition.

Results: Analysis of variance ($P < 0.05$) showed statistically significant pre versus post-test differences in lean mass (pre 45.80 kg vs. post 46.28 kg at $P = 0.011$) and close to statistically significant pre- versus post-test differences in upper body strength (pre 28.91 kg vs. post 30.82 kg at $P = 0.052$) and lower body strength (pre 87.64 kg vs. post 96.08 kg at $P = 0.056$). There was no significant difference in the lower and upper body flexibility, total mass, fat mass and bone density pre and post mean values.

Conclusions: Essentrics improved total body lean mass and may improve lower and upper body strength.

Zhang Y, Wu J, Xiao N, Li B. Hyperbaric Oxygen Therapy Is Beneficial for the Improvement of Clinical Symptoms of Cerebral Palsy: A Systematic Review and Meta-Analysis. *Complementary Medicine Research: 2022;* 29(2): 158-71p.

Abstract:

Introduction: Hyperbaric oxygen (HBO) has been used for the treatment of cerebral palsy for more than 20 years, but its efficacy and safety are still controversial. In this systematic review and meta-analysis, we evaluated the currently promulgated data related to the efficacy of HBO for patients with cerebral palsy.

Methods: We searched the PubMed/Medline, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, and Wanfang databases (from their inception to April 2020) for randomized controlled trials published in English or Chinese. Two researchers used the Cochrane Collaboration tool for data extraction and an independent quality assessment. The extracted data were analyzed by Review Manager 5.3 software.

Results: A total of 25 studies consistent with the inclusion criteria were included, with a total of 2,146 people, which included 1,185 participants in the HBO group and 961 in the control group. This meta-analysis showed that when compared with the controls, HBO therapy can improve the gross motor functions evaluated by the Gross Motor Function Measure (n = 696, SMD 0.29, 95% CI [0.07–0.51], Z = 2.62, p = 0.009) and Gross Motor Function Classification System (n = 248, MD –0.40, 95% CI [–0.52 to –0.27], Z = 6.28, p < 0.00001), global developmental level evaluated by Gesell (n = 560, RR 1.30, 95% CI [1.19–1.42], Z = 6.03, p < 0.00001) and developmental quotient (n = 374, MD 8.25, 95% CI [6.48–10.01], Z = 9.15, p < 0.00001) and language expression (n = 270, MD 4.34, 95% CI [2.30–6.38], Z = 4.17, p < 0.00001) and comprehension (n = 270, MD 4.87, 95% CI [2.87–6.88], Z = 4.76, p < 0.00001). HBO therapy only caused mild ear pain. However, the quality of the data for all outcomes evaluated by the Grading of Recommendations Assessment, Development, and Evaluation analysis was very low.

Conclusions: HBO therapy may produce a much more efficient clinical experiment result than the control group with cerebral palsy patients, and HBO therapy is well tolerated and relatively safe for the included participants.

Zheng Xinyi, Wang Fangfang, Liu Chang, Gu Jianghong, Qu Fan. Effects of Chinese Herbal Medicine on ovarian functions in the patients with endometriosis: A systematic review and meta-analysis of randomized controlled trials. *European Journal of Integrative Medicine: 2022;* 51: Article 102125

Abstract:

Introduction: When using Chinese Herbal Medicine (CHM) to treat endometriosis, the effects of CHM on the ovarian function have received little attention. This systematic review and meta-analysis aimed to evaluate the effects and safety of CHM on the ovarian function in patients with endometriosis.

Methods: Eight electronic databases were searched from their inception to March 2, 2021. We compared those receiving CHM with controls, all studies included were randomized controlled trials (RCTs). Statistical analysis was performed using standard mean difference of hormonal levels: Estradiol(E2), Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH). Subgroup analysis and sensitivity analysis were conducted.

Results: A total of 844 patients from 11 RCTs were included. In E2 levels, the analysis revealed a significant effect in favor of CHM group comparedwith the control group (SMD = 3.05, 95%CI = 0.29 to 1.32, P = 0.002). After subgroup analyses, there were still significant effects in both non-operative subgroup (SMD = 2.04, 95%CI = 0.04 to 1.88, P = 0.04) and post-operative subgroup (SMD = 2.19, 95%CI = 0.08 to 1.42, P = 0.03). There were no significant differences between the two subgroups in both FSH levels (P > 0.05) and LH levels (P > 0.05), and the subgroup analyses showed similar results. No adverse events were reported.

Conclusions: CHM may improve ovarian function in patients with endometriosis through increasing E2 levels whether there is surgery or not, which may indicate a referable and safe treatment of endometriosis. Due to the weak evidence, high-quality clinical trials are needed to support this conclusion.

Allied System of Medicine

Bergmark Brian A, Mathenge Njambi, Merlini Piera A, Lawrence-Wright Marilyn B, Giugliano Robert P. Acute coronary syndromes. *Lancet 2022;* 399(10332): 1347-58p.

Abstract:

Although substantial progress has been made in the diagnosis and treatment of acute coronary syndromes, cardiovascular disease remains the leading cause of death globally, with nearly half of these deaths due to ischaemic heart disease. The broadening availability of high-sensitivity troponin assays has allowed for rapid rule-out algorithms in patients with suspected non-ST-segment elevated myocardial infarction (NSTEMI). Dual antiplatelet therapy is recommended for 12 months following an acute coronary syndrome in most patients, and additional secondary prevention measures including intensive lipid-lowering therapy (LDL-C <1·4 mmol/L), neurohormonal agents, and lifestyle modification, are crucial. The scientific evidence for diagnosis and management of acute coronary syndromes continues to evolve rapidly, including adapting to the COVID-19 pandemic, which has impacted all aspects of care. This Seminar provides a clinically relevant overview of the pathobiology, diagnosis, and management of acute coronary syndromes, and describes key scientific advances.

Bollyky Thomas J, Hulland Erin N, Barber Ryan M, Collins James K, Dieleman Joseph L. Pandemic preparedness and COVID-19: An exploratory analysis of infection and fatality rates, and contextual factors associated with preparedness in 177 countries, from Jan 1, 2020, to Sept 30, 2021. *Lancet 2022;* 399(10334): 1489-1512p.

Abstract:

Background: National rates of COVID-19 infection and fatality have varied dramatically since the onset of the pandemic. Understanding the conditions associated with this cross-country variation is essential to guiding investment in more effective preparedness and response for future pandemics.

Methods: Daily SARS-CoV-2 infections and COVID-19 deaths for 177 countries and territories and 181 subnational locations were extracted from the Institute for Health Metrics and Evaluation's modelling database. Cumulative infection rate and infection-fatality ratio (IFR) were estimated and standardised for environmental, demographic, biological, and economic factors. For infections, we included factors associated with environmental seasonality (measured as the relative risk of pneumonia), population density, gross domestic product (GDP) per capita, proportion of the population living below 100 m, and a proxy for previous exposure to other betacoronaviruses. For IFR, factors were age distribution of the population,

mean body-mass index (BMI), exposure to air pollution, smoking rates, the proxy for previous exposure to other betacoronaviruses, population density, age-standardised prevalence of chronic obstructive pulmonary disease and cancer, and GDP per capita. These were standardised using indirect age standardisation and multivariate linear models. Standardised national cumulative infection rates and IFRs were tested for associations with 12 pandemic preparedness indices, seven health-care capacity indicators, and ten other demographic, social, and political conditions using linear regression. To investigate pathways by which important factors might affect infections with SARS-CoV-2, we also assessed the relationship between interpersonal and governmental trust and corruption and changes in mobility patterns and COVID-19 vaccination rates.

Findings: The factors that explained the most variation in cumulative rates of SARS-CoV-2 infection between Jan 1, 2020, and Sept 30, 2021, included the proportion of the population living below 100 m (5·4% [4·0–7·9] of variation), GDP per capita (4·2% [1·8–6·6] of variation), and the proportion of infections attributable to seasonality (2·1% [95% uncertainty interval 1·7–2·7] of variation). Most cross-country variation in cumulative infection rates could not be explained. The factors that explained the most variation in COVID-19 IFR over the same period were the age profile of the country (46·7% [18·4–67·6] of variation), GDP per capita (3·1% [0·3–8·6] of variation), and national mean BMI (1·1% [0·2–2·6] of variation). 44·4% (29·2–61·7) of cross-national variation in IFR could not be explained. Pandemic-preparedness indices, which aim to measure health security capacity, were not meaningfully associated with standardised infection rates or IFRs. Measures of trust in the government and interpersonal trust, as well as less government corruption, had larger, statistically significant associations with lower standardised infection rates. High levels of government and interpersonal trust, as well as less government corruption, were also associated with higher COVID-19 vaccine coverage among middle-income and high-income countries where vaccine availability was more widespread, and lower corruption was associated with greater reductions in mobility. If these modelled associations were to be causal, an increase in trust of governments such that all countries had societies that attained at least the amount of trust in government or interpersonal trust measured in Denmark, which is in the 75th percentile across these spectrums, might have reduced global infections by 12·9% (5·7–17·8) for government trust and 40·3% (24·3–51·4) for interpersonal trust. Similarly, if all countries had a national BMI equal to or less than that of the 25th percentile, our analysis suggests global standardised IFR would be reduced by 11·1%.

Interpretation: Efforts to improve pandemic preparedness and response for the next pandemic might benefit from greater investment in risk communication and community engagement strategies to boost the confidence that individuals have in public health guidance. Our results suggest that increasing health promotion for key modifiable risks is associated with a reduction of fatalities in such a scenario.

Funding: Bill & Melinda Gates Foundation, J Stanton, T Gillespie, J and E Nordstrom, and Bloomberg Philanthropies.

Cancer care: Beyond survival. *Lancet 2022;* 399(10334): 1441p.

Cousins Sophie. Afghanistan's health crisis deepens under the Taliban *Lancet 2022;* 399(10332): 1290-91p.

Crosbie Emma J, Kitson Sarah J, McAlpine Jessica N, Mukhopadhyay Asima, Singh Naveena. Endometrial cancer. *Lancet 2022;* 399(10333): 1412-28p.

Abstract:

Endometrial cancer is the most common gynaecological cancer in high income countries and its incidence is rising globally. Although an ageing population and fewer benign hysterectomies have contributed to this trend, the growing prevalence of obesity is the major underlying cause. Obesity poses challenges for diagnosis and treatment and more research is needed to offer primary prevention to high-risk women and to optimise endometrial cancer survivorship. Early presentation with postmenopausal bleeding ensures most endometrial cancers are cured by hysterectomy but those with advanced disease have a poor prognosis. Minimally invasive surgical staging and sentinel-lymph-node biopsy provides a low morbidity alternative to historical surgical management without compromising oncological outcomes. Adjuvant radiotherapy reduces loco-regional recurrence in intermediate-risk and high-risk cases. Advances in our understanding of the molecular biology of endometrial cancer have paved the way for targeted chemotherapeutic strategies, and clinical trials will establish their benefit in adjuvant, advanced, and recurrent disease settings in the coming years.

Devi Sharmila. Medical crisis for Rohingya refugees. *Lancet 2022;* 399(10334): 1458p.

Emery Jon, Butow Phyllis, Lai Kwon Julia, Nekhlyudov Larissa, Jefford Michael. Management of common clinical problems experienced by survivors of cancer. *Lancet 2022;* 399(10334): 1537-50p.

Abstract:

Improvements in early detection and treatment have led to a growing prevalence of survivors of cancer worldwide. Models of care fail to address adequately the breadth of physical, psychosocial, and supportive care needs of those who survive cancer. In this Series paper, we summarise the evidence around the management of common clinical problems experienced by survivors of adult cancers and how to cover these issues in a consultation. Reviewing the patient's history of cancer and treatments highlights potential long-term or late effects to consider, and recommended surveillance for recurrence. Physical consequences of specific treatments to

identify include cardiac dysfunction, metabolic syndrome, lymphoedema, peripheral neuropathy, and osteoporosis. Immunotherapies can cause specific immune-related effects most commonly in the gastrointestinal tract, endocrine system, skin, and liver. Pain should be screened for and requires assessment of potential causes and non-pharmacological and pharmacological approaches to management. Common psychosocial issues, for which there are effective psychological therapies, include fear of recurrence, fatigue, altered sleep and cognition, and effects on sex and intimacy, finances, and employment. Review of lifestyle factors including smoking, obesity, and alcohol is necessary to reduce the risk of recurrence and second cancers. Exercise can improve quality of life and might improve cancer survival; it can also contribute to the management of fatigue, pain, metabolic syndrome, osteoporosis, and cognitive impairment. Using a supportive care screening tool, such as the Distress Thermometer, can identify specific areas of concern and help prioritise areas to cover in a consultation.

Ezekowitz Justin A, Colin Ramirez Eloisa, Ross Heather, Escobedo Jorge, Zieroth Shelley. Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): An international, open-label, randomised, controlled trial. *Lancet 2022;* 399(10333): 1391-1400p.

Abstract:

Background: Dietary restriction of sodium has been suggested to prevent fluid overload and adverse outcomes for patients with heart failure. We designed the Study of Dietary Intervention under 100 mmol in Heart Failure (SODIUM-HF) to test whether or not a reduction in dietary sodium reduces the incidence of future clinical events.

Methods: SODIUM-HF is an international, open-label, randomised, controlled trial that enrolled patients at 26 sites in six countries (Australia, Canada, Chile, Colombia, Mexico, and New Zealand). Eligible patients were aged 18 years or older, with chronic heart failure (New York Heart Association [NYHA] functional class 2–3), and receiving optimally tolerated guideline-directed medical treatment. Patients were randomly assigned (1:1), using a standard number generator and varying block sizes of two, four, or six, stratified by site, to either usual care according to local guidelines or a low sodium diet of less than 100 mmol (ie, <1500 mg/day). The primary outcome was the composite of cardiovascular-related admission to hospital, cardiovascular-related emergency department visit, or all-cause death within 12 months in the intention-to-treat (ITT) population (ie, all randomly assigned patients). Safety was assessed in the ITT population. This study is registered with ClinicalTrials.gov, NCT02012179, and is closed to accrual.

Findings: Between March 24, 2014, and Dec 9, 2020, 806 patients were randomly assigned to a low sodium diet (n=397) or usual care (n=409). Median age was 67 years (IQR 58–74) and 268 (33%) were women and 538 (66%) were men. Between baseline and 12 months, the median sodium

intake decreased from 2286 mg/day (IQR 1653–3005) to 1658 mg/day (1301–2189) in the low sodium group and from 2119 mg/day (1673–2804) to 2073 mg/day (1541–2900) in the usual care group. By 12 months, events comprising the primary outcome had occurred in 60 (15%) of 397 patients in the low sodium diet group and 70 (17%) of 409 in the usual care group (hazard ratio [HR] 0·89 [95% CI 0·63–1·26]; p=0·53). All-cause death occurred in 22 (6%) patients in the low sodium diet group and 17 (4%) in the usual care group (HR 1·38 [0·73–2·60]; p=0·32), cardiovascular-related hospitalisation occurred in 40 (10%) patients in the low sodium diet group and 51 (12%) patients in the usual care group (HR 0·82 [0·54–1·24]; p=0·36), and cardiovascular-related emergency department visits occurred in 17 (4%) patients in the low sodium diet group and 15 (4%) patients in the usual care group (HR 1·21 [0·60–2·41]; p=0·60). No safety events related to the study treatment were reported in either group.

Interpretation: In ambulatory patients with heart failure, a dietary intervention to reduce sodium intake did not reduce clinical events.

Funding: Canadian Institutes of Health Research and the University Hospital Foundation, Edmonton, Alberta, Canada, and Health Research Council of New Zealand.

Farzadfar Farshad, Naghavi Mohsen, Sepanlou Sadaf G, Moghaddam Sahar Saeedi, Larijani Bagher. Health system performance in Iran: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet 2022;* 399(10335): 1625-45p.

Abstract:

Background: Better evaluation of existing health programmes, appropriate policy making against emerging health threats, and reducing inequalities in Iran rely on a comprehensive national and subnational breakdown of the burden of diseases, injuries, and risk factors.

Methods: In this systematic analysis, we present the national and subnational estimates of the burden of disease in Iran using the Global Burden of Disease Study 2019. We report trends in demographics, all-cause and cause-specific mortality, as well as years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs) caused by major diseases and risk factors. A multi-intervention segmented-regression model was used to explore the overall impact of health sector changes and sanctions. For this analysis, we used a variety of sources and reports, including vital registration, census, and survey data to provide estimates of mortality and morbidity at the national and subnational level in Iran.

Findings: Iran, which had 84·3 million inhabitants in 2019, had a life expectancy of 79·6 years (95% uncertainty interval 79·2–79·9) in female individuals and 76·1 (75·6–76·5) in male individuals, an increase compared with 1990. The number of DALYs remained stable and reached 19·8 million (17·3–22·6) in 2019, of which 78·1% were caused by non-communicable

diseases (NCDs) compared with 43·0% in 1990. During the study period, age-standardised DALY rates and YLL rates decreased considerably; however, YLDs remained nearly constant. The share of age-standardised YLDs contributing to the DALY rate steadily increased to 44·5% by 2019. With regard to the DALY rates of different provinces, inequalities were decreasing. From 1990 to 2019, although the number of DALYs attributed to all risk factors decreased by 16·8%, deaths attributable to all risk factors substantially grew by 43·8%. The regression results revealed a significant negative association between sanctions and health status.

Interpretation: The Iranian health-care system is encountering NCDs as its new challenge, which necessitates a coordinated multisectoral approach. Although the Iranian health-care system has been successful to some extent in controlling mortality, it has overlooked the burden of morbidity and need for rehabilitation. We did not capture alleviation of the burden of diseases in Iran following the 2004 and 2014 health sector reforms; however, the sanctions were associated with deaths of Iranians caused by NCDs.

Funding: Bill & Melinda Gates Foundation.

Jefford Michael, Howell Doris, Li Qiuping, Lisy Karolina, Emery Jon. Improved models of care for cancer survivors. *Lancet 2022;* 399(10334): 1551-60p.

Abstract:

The number of survivors of cancer is increasing substantially. Current models of care are unsustainable and fail to address the many unmet needs of survivors of cancer. Numerous trials have investigated alternate models of care, including models led by primary-care providers, care shared between oncology specialists and primary-care providers, and care led by oncology nurses. These alternate models appear to be at least as effective as specialist-led care and are applicable to many survivors of cancer. Choosing the most appropriate care model for each patient depends on patient-level factors (such as risk of longer-term effects, late effects, individual desire, and capacity to self-manage), local services, and health-care policy. Wider implementation of alternative models requires appropriate support for non-oncologist care providers and endorsement of these models by cancer teams with their patients. The COVID-19 pandemic has driven some changes in practice that are more patient-centred and should continue. Improved models should shift from a predominant focus on detection of cancer recurrence and seek to improve the quality of life, functional outcomes, experience, and survival of survivors of cancer, reduce the risk of recurrence and new cancers, improve the management of comorbidities, and reduce costs to patients and payers. This Series paper focuses primarily on high-income countries, where most data have been derived. However, future research should consider the applicability of these models in a wider range of health-care settings and for a wider range of cancers.

Kanungo Suman, Azman Andrew S, Ramamurthy Thandavarayan, Deen Jaqueline, Dutta Shanta. Cholera. *Lancet 2022;* 399(10333): 1429-40p.

Abstract:

Cholera was first described in the areas around the Bay of Bengal and spread globally, resulting in seven pandemics during the past two centuries. It is caused by toxigenic *Vibrio cholerae* O1 or O139 bacteria. Cholera is characterised by mild to potentially fatal acute watery diarrhoeal disease. Prompt rehydration therapy is the cornerstone of management. We present an overview of cholera and its pathogenesis, natural history, bacteriology, and epidemiology, while highlighting advances over the past 10 years in molecular epidemiology, immunology, and vaccine development and deployment. Since 2014, the Global Task Force on Cholera Control, a WHO coordinated network of partners, has been working with several countries to develop national cholera control strategies. The global roadmap for cholera control focuses on stopping transmission in cholera hotspots through vaccination and improved water, sanitation, and hygiene, with the aim to reduce cholera deaths by 90% and eliminate local transmission in at least 20 countries by 2030.

Khobragade Akash, Bhate Suresh, Ramaiah Vijendra, Deshpande Shrikant, Koradia Parshottam. Efficacy, safety, and immunogenicity of the DNA SARS-CoV-2 vaccine (ZyCoV-D): The interim efficacy results of a phase 3, randomised, double-blind, placebo-controlled study in India. *Lancet 2022;* 399(10332): 1313-21p.

Abstract:

Background: ZyCoV-D, a DNA-based vaccine, showed promising safety and immunogenicity in a phase 1/2 trial. We now report the interim efficacy results of phase 3 clinical trial with ZyCoV-D vaccine in India.

Methods: We conducted an interim analysis of a multicentre, double-blind, randomised, placebo-controlled phase 3 trial at 49 centres in India. Healthy participants aged at least 12 years were enrolled and randomly assigned (1:1) to receive either ZyCov-D vaccine (Cadila Healthcare; 2 mg per dose) or placebo. An interactive web response system was used for randomisation (blocks of four) of participants as well as to enrol those aged 60 years and older with or without comorbid conditions, and those aged 12–17 years. It was also used to identify 600 participants for immunogenicity (blocks of six). Participants, investigators, and outcome assessors were masked to treatment assignment. Three doses of vaccine or placebo were administered intradermally via a needle-free injection system 28 days apart. The primary outcome was the number of participants with first occurrence of symptomatic RT-PCR-positive COVID-19 28 days after the third dose, until the targeted number of cases (interim analysis n=79, full analysis n=158) have been achieved. The analysis was done in the per-protocol population, which consisted of all participants with negative baseline SARS-CoV-2 status who received three doses of vaccine or placebo. Assessment of safety

and tolerability was based on the safety population, which consisted of all enrolled participants who were known to have received at least one dose of study vaccine or placebo. This trial is registered with Clinical Trial Registry India, CTRI/2021/01/030416, and is ongoing.

Findings: Between Jan 16, and June 23, 2021 (data cutoff), 33 194 individuals were screened, of whom 5241 did not meet screening criteria and 27 703 were enrolled and randomly assigned to receive ZyCoV-D (n=13 851) or placebo (n=13 852). Per-protocol, 81 cases were eligible and included in efficacy analysis (20 of 12 350 in the ZyCoV-D group and 61 of 12 320 in placebo group). The ZyCoV-D vaccine efficacy was found to be 66·6% (95% CI 47·6–80·7). The occurrence of solicited adverse events was similar between the treatment groups (623 [4·49%] in the ZyCoV-D group vs 620 [4·47%] in the placebo group). There were two deaths (one in each group) reported at the data cutoff, neither of which was considered related to the study treatments.

Interpretation: In this interim analysis, ZyCoV-D vaccine was found to be efficacious, safe, and immunogenic in a phase 3 trial.

Funding: National Biopharma Mission, Department of Biotechnology, Government of India and Cadila Healthcare, Ahmedabad, Gujarat India.

Mahfoud Felix, Kandzari David E, Kario Kazuomi, Townsend Raymond R, Bohm Michael. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): A randomised, sham-controlled trial. *Lancet 2022;* 399(10333): 1401-10p.

Abstract:

Background: Renal denervation has been shown to lower blood pressure in the presence of antihypertensive medications; however, long-term safety and efficacy data from randomised trials of renal denervation are lacking. In this pre-specified analysis of the SPYRAL HTN-ON MED study, we compared changes in blood pressure, antihypertensive drug use, and safety up to 36 months in renal denervation versus a sham control group.

Methods: This randomised, single-blind, sham-controlled trial enrolled patients from 25 clinical centres in the USA, Germany, Japan, the UK, Australia, Austria, and Greece, with uncontrolled hypertension and office systolic blood pressure between 150 mm Hg and 180 mm Hg and diastolic blood pressure of 90 mm Hg or higher. Eligible patients had to have 24-h ambulatory systolic blood pressure between 140 mm Hg and less than 170 mm Hg, while taking one to three antihypertensive drugs with stable doses for at least 6 weeks. Patients underwent renal angiography and were randomly assigned (1:1) to radiofrequency renal denervation or a sham control procedure. Patients and physicians were unmasked after 12-month follow-up and sham control patients could cross over after 12-month follow-up completion. The primary endpoint was the treatment difference in mean

24-h systolic blood pressure at 6 months between the renal denervation group and the sham control group. Statistical analyses were done on the intention-to-treat population. Long-term efficacy was assessed using ambulatory and office blood pressure measurements up to 36 months. Drug surveillance was used to assess medication use. Safety events were assessed up to 36 months. This trial is registered with ClinicalTrials.gov, NCT02439775; prospectively, an additional 260 patients are currently being randomly assigned as part of the SPYRAL HTN-ON MED Expansion trial.

Findings: Between July 22, 2015, and June 14, 2017, among 467 enrolled patients, 80 patients fulfilled the qualifying criteria and were randomly assigned to undergo renal denervation (n=38) or a sham control procedure (n=42). Mean ambulatory systolic and diastolic blood pressure were significantly reduced from baseline in the renal denervation group, and were significantly lower than the sham control group at 24 and 36 months, despite a similar treatment intensity of antihypertensive drugs. The medication burden at 36 months was 2·13 medications (SD 1·15) in the renal denervation group and 2·55 medications (2·19) in the sham control group (p=0·26). 24 (77%) of 31 patients in the renal denervation group and 25 (93%) of 27 patients in the sham control group adhered to medication at 36 months. At 36 months, the ambulatory systolic blood pressure reduction was −18·7 mm Hg (SD 12·4) for the renal denervation group (n=30) and −8·6 mm Hg (14·6) for the sham control group (n=32; adjusted treatment difference −10·0 mm Hg, 95% CI −16·6 to −3·3; p=0·0039). Treatment differences between the renal denervation group and sham control group at 36 months were −5·9 mm Hg (95% CI −10·1 to −1·8; p=0·0055) for mean ambulatory diastolic blood pressure, −11·0 mm Hg (−19·8 to −2·1; p=0·016) for morning systolic blood pressure, and −11·8 mm Hg (−19·0 to −4·7; p=0·0017) for night-time systolic blood pressure. There were no short-term or long-term safety issues associated with renal denervation.

Interpretation: Radiofrequency renal denervation compared with sham control produced a clinically meaningful and lasting blood pressure reduction up to 36 months of follow-up, independent of concomitant antihypertensive medications and without major safety events. Renal denervation could provide an adjunctive treatment modality in the management of patients with hypertension.

Funding: Medtronic.

Makoni Munyaradzi. Hope for access to abortion in Kenya. *Lancet 2022;* 399(10334): 1456p.

Malaria in 2022: A year of opportunity. *Lancet 2022;* 399(10335): 1573p.

Menni Cristina, Valdes Ana M, Polidori Lorenzo, Antonelli Michela, Spector Tim D. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of

omicron and delta variant dominance: A prospective observational study from the ZOE COVID Study. *Lancet 2022;* 399(10335): 1618-24p.

Abstract:

Background: The SARS-CoV-2 variant of concern, omicron, appears to be less severe than delta. We aim to quantify the differences in symptom prevalence, risk of hospital admission, and symptom duration among the vaccinated population.

Methods: In this prospective longitudinal observational study, we collected data from participants who were self-reporting test results and symptoms in the ZOE COVID app (previously known as the COVID Symptoms Study App). Eligible participants were aged 16–99 years, based in the UK, with a body-mass index between 15 and 55 kg/m2, had received at least two doses of any SARS-CoV-2 vaccine, were symptomatic, and logged a positive symptomatic PCR or lateral flow result for SARS-CoV-2 during the study period. The primary outcome was the likelihood of developing a given symptom (of the 32 monitored in the app) or hospital admission within 7 days before or after the positive test in participants infected during omicron prevalence compared with those infected during delta prevalence.

Findings: Between June 1, 2021, and Jan 17, 2022, we identified 63 002 participants who tested positive for SARS-CoV-2 and reported symptoms in the ZOE app. These patients were matched 1:1 for age, sex, and vaccination dose, across two periods (June 1 to Nov 27, 2021, delta prevalent at >70%; n=4990, and Dec 20, 2021, to Jan 17, 2022, omicron prevalent at >70%; n=4990). Loss of smell was less common in participants infected during omicron prevalence than during delta prevalence (16·7% vs 52·7%, odds ratio [OR] 0·17; 95% CI 0·16–0·19, p<0·001). Sore throat was more common during omicron prevalence than during delta prevalence (70·5% vs 60·8%, 1·55; 1·43–1·69, p<0·001). There was a lower rate of hospital admission during omicron prevalence than during delta prevalence (1·9% vs 2·6%, OR 0·75; 95% CI 0·57–0·98, p=0·03).

Interpretation: The prevalence of symptoms that characterise an omicron infection differs from those of the delta SARS-CoV-2 variant, apparently with less involvement of the lower respiratory tract and reduced probability of hospital admission. Our data indicate a shorter period of illness and potentially of infectiousness which should impact work–health policies and public health advice.

Funding: Wellcome Trust, ZOE, National Institute for Health Research, Chronic Disease Research Foundation, National Institutes of Health, and Medical Research Council.

Misganaw Awoke, Naghavi Mohsen, Walker Ally, Mirkuzie Alemnesh H, Gebremedhin Lia Tadesse. Progress in health among regions of Ethiopia, 1990–2019: A subnational country analysis for the Global Burden of Disease Study 2019. *Lancet 2022;* 399(10332): 1322-35p.

Abstract:

Background: Previous Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) studies have reported national health estimates for Ethiopia. Substantial regional variations in socioeconomic status, population, demography, and access to health care within Ethiopia require comparable estimates at the subnational level. The GBD 2019 Ethiopia subnational analysis aimed to measure the progress and disparities in health across nine regions and two chartered cities.

Methods: We gathered 1057 distinct data sources for Ethiopia and all regions and cities that included census, demographic surveillance, household surveys, disease registry, health service use, disease notifications, and other data for this analysis. Using all available data sources, we estimated the Socio-demographic Index (SDI), total fertility rate (TFR), life expectancy, years of life lost, years lived with disability, disability-adjusted life-years, and risk-factor-attributable health loss with 95% uncertainty intervals (UIs) for Ethiopia's nine regions and two chartered cities from 1990 to 2019. Spatiotemporal Gaussian process regression, cause of death ensemble model, Bayesian meta-regression tool, DisMod-MR 2.1, and other models were used to generate fertility, mortality, cause of death, and disability rates. The risk factor attribution estimations followed the general framework established for comparative risk assessment.

Findings: The SDI steadily improved in all regions and cities from 1990 to 2019, yet the disparity between the highest and lowest SDI increased by 54% during that period. The TFR declined from 6·91 (95% UI 6·59–7·20) in 1990 to 4·43 (4·01–4·92) in 2019, but the magnitude of decline also varied substantially among regions and cities. In 2019, TFR ranged from 6·41 (5·96–6·86) in Somali to 1·50 (1·26–1·80) in Addis Ababa. Life expectancy improved in Ethiopia by 21·93 years (21·79–22·07), from 46·91 years (45·71–48·11) in 1990 to 68·84 years (67·51–70·18) in 2019. Addis Ababa had the highest life expectancy at 70·86 years (68·91–72·65) in 2019; Afar and Benishangul-Gumuz had the lowest at 63·74 years (61·53–66·01) for Afar and 64.28 (61.99-66.63) for Benishangul-Gumuz. The overall increases in life expectancy were driven by declines in under-5 mortality and mortality from common infectious diseases, nutritional deficiency, and war and conflict. In 2019, the age-standardised all-cause death rate was the highest in Afar at 1353·38 per 100 000 population (1195·69–1526·19). The leading causes of premature mortality for all sexes in Ethiopia in 2019 were neonatal disorders, diarrhoeal diseases, lower respiratory infections, tuberculosis, stroke, HIV/AIDS, ischaemic heart disease, cirrhosis, congenital defects, and diabetes. With high SDIs and life expectancy for all sexes, Addis Ababa, Dire Dawa, and Harari had low rates of premature mortality from the five leading causes, whereas regions with low SDIs and life expectancy for all sexes (Afar and Somali) had high rates of premature mortality from the leading causes. In 2019, child and maternal malnutrition; unsafe water, sanitation, and handwashing; air pollution;

high systolic blood pressure; alcohol use; and high fasting plasma glucose were the leading risk factors for health loss across regions and cities.

Interpretation: There were substantial improvements in health over the past three decades across regions and chartered cities in Ethiopia. However, the progress, measured in SDI, life expectancy, TFR, premature mortality, disability, and risk factors, was not uniform. Federal and regional health policy makers should match strategies, resources, and interventions to disease burden and risk factors across regions and cities to achieve national and regional plans, Sustainable Development Goals, and universal health coverage targets.

Funding: Bill & Melinda Gates Foundation.

Nyberg Tommy, Ferguson Neil M, Nash Sophie G, Webster Harriet H, Thelwall Simon. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: A cohort study. *Lancet 2022;* 399(10332): 1303-12p.

Abstract:

Background: The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine escape and high transmissibility, with early studies indicating lower severity of infection than that of the delta variant (B.1.617.2). We aimed to better characterise omicron severity relative to delta by assessing the relative risk of hospital attendance, hospital admission, or death in a large national cohort.

Methods: Individual-level data on laboratory-confirmed COVID-19 cases resident in England between Nov 29, 2021, and Jan 9, 2022, were linked to routine datasets on vaccination status, hospital attendance and admission, and mortality. The relative risk of hospital attendance or admission within 14 days, or death within 28 days after confirmed infection, was estimated using proportional hazards regression. Analyses were stratified by test date, 10-year age band, ethnicity, residential region, and vaccination status, and were further adjusted for sex, index of multiple deprivation decile, evidence of a previous infection, and year of age within each age band. A secondary analysis estimated variant-specific and vaccine-specific vaccine effectiveness and the intrinsic relative severity of omicron infection compared with delta (ie, the relative risk in unvaccinated cases).

Findings: The adjusted hazard ratio (HR) of hospital attendance (not necessarily resulting in admission) with omicron compared with delta was 0·56 (95% CI 0·54–0·58); for hospital admission and death, HR estimates were 0·41 (0·39–0·43) and 0·31 (0·26–0·37), respectively. Omicron versus delta HR estimates varied with age for all endpoints examined. The adjusted HR for hospital admission was 1·10 (0·85–1·42) in those younger than 10 years, decreasing to 0·25 (0·21–0·30) in 60–69-year-olds, and then increasing to 0·47 (0·40–0·56) in those aged at least 80 years. For both

variants, past infection gave some protection against death both in vaccinated (HR 0·47 [0·32–0·68]) and unvaccinated (0·18 [0·06–0·57]) cases. In vaccinated cases, past infection offered no additional protection against hospital admission beyond that provided by vaccination (HR 0·96 [0·88–1·04]); however, for unvaccinated cases, past infection gave moderate protection (HR 0·55 [0·48–0·63]). Omicron versus delta HR estimates were lower for hospital admission (0·30 [0·28–0·32]) in unvaccinated cases than the corresponding HR estimated for all cases in the primary analysis. Booster vaccination with an mRNA vaccine was highly protective against hospitalisation and death in omicron cases (HR for hospital admission 8–11 weeks post-booster vs unvaccinated: 0·22 [0·20–0·24]), with the protection afforded after a booster not being affected by the vaccine used for doses 1 and 2.

Interpretation: The risk of severe outcomes following SARS-CoV-2 infection is substantially lower for omicron than for delta, with higher reductions for more severe endpoints and significant variation with age. Underlying the observed risks is a larger reduction in intrinsic severity (in unvaccinated individuals) counterbalanced by a reduction in vaccine effectiveness. Documented previous SARS-CoV-2 infection offered some protection against hospitalisation and high protection against death in unvaccinated individuals, but only offered additional protection in vaccinated individuals for the death endpoint. Booster vaccination with mRNA vaccines maintains over 70% protection against hospitalisation and death in breakthrough confirmed omicron infections.

Funding: Medical Research Council, UK Research and Innovation, Department of Health and Social Care, National Institute for Health Research, Community Jameel, and Engineering and Physical Sciences Research Council.

Ockenden review and women's health in the UK. *Lancet 2022;* 399(10333): 1359p.

Offshoring the asylum process: A dangerous move for health. *Lancet 2022;* 399(10336): 1669p.

Piccini Jonathan P, Caso Valeria, Connolly Stuart J, Fox Keith AA, Child Nick. Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): A multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. *Lancet 2022;* 399(10333): 1383-90p.

Abstract:

Background: Direct-acting oral anticoagulant use for stroke prevention in atrial fibrillation is limited by bleeding concerns. Asundexian, a novel, oral small molecule activated coagulation factor XIa (FXIa) inhibitor, might reduce thrombosis with minimal effect on haemostasis. We aimed to

determine the optimal dose of asundexian and to compare the incidence of bleeding with that of apixaban in patients with atrial fibrillation.

Methods: In this randomised, double-blind, phase 2 dose-finding study, we compared asundexian 20 mg or 50 mg once daily with apixaban 5 mg twice daily in patients aged 45 years or older with atrial fibrillation, a CHA2DS2-VASc score of at least 2 if male or at least 3 if female, and increased bleeding risk. The study was conducted at 93 sites in 14 countries, including 12 European countries, Canada, and Japan. Participants were randomly assigned (1:1:1) to a treatment group using an interactive web response system, with randomisation stratified by whether patients were receiving a direct-acting oral anticoagulant before the study start. Masking was achieved using a double-dummy design, with participants receiving both the assigned treatment and a placebo that resembled the non-assigned treatment. The primary endpoint was the composite of major or clinically relevant non-major bleeding according to International Society on Thrombosis and Haemostasis criteria, assessed in all patients who took at least one dose of study medication. This trial is registered with ClinicalTrials.gov, NCT04218266, and EudraCT, 2019-002365-35.

Findings: Between Jan 30, 2020, and June 21, 2021, 862 patients were enrolled. 755 patients were randomly assigned to treatment. Two patients (assigned to asundexian 20 mg) never took any study medication, resulting in 753 patients being included in the analysis (249 received asundexian 20 mg, 254 received asundexian 50 g, and 250 received apixaban). The mean age of participants was 73·7 years (SD 8·3), 309 (41%) were women, 216 (29%) had chronic kidney disease, and mean CHA2DS2-VASc score was 3·9 (1·3). Asundexian 20 mg resulted in 81% inhibition of FXIa activity at trough concentrations and 90% inhibition at peak concentrations; asundexian 50 mg resulted in 92% inhibition at trough concentrations and 94% inhibition at peak concentrations. Ratios of incidence proportions for the primary endpoint were 0·50 (90% CI 0·14–1·68) for asundexian 20 mg (three events), 0·16 (0·01–0·99) for asundexian 50 mg (one event), and 0·33 (0·09–0·97) for pooled asundexian (four events) versus apixaban (six events). The rate of any adverse event occurring was similar in the three treatment groups: 118 (47%) with asundexian 20 mg, 120 (47%) with asundexian 50 mg, and 122 (49%) with apixaban.

Interpretation: The FXIa inhibitor asundexian at doses of 20 mg and 50 mg once daily resulted in lower rates of bleeding compared with standard dosing of apixaban, with near-complete in-vivo FXIa inhibition, in patients with atrial fibrillation.

Funding: Bayer.

Saji Hisashi, Okada Morihito, Tsuboi Masahiro, Nakajima Ryu, Asamura Hisao. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): A multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. ***Lancet 2022;*** **399(10335): 1607-17p.**

Abstract:

Background: Lobectomy is the standard of care for early-stage non-small-cell lung cancer (NSCLC). The survival and clinical benefits of segmentectomy have not been investigated in a randomised trial setting. We aimed to investigate if segmentectomy was non-inferior to lobectomy in patients with small-sized peripheral NSCLC.

Methods: We conducted this randomised, controlled, non-inferiority trial at 70 institutions in Japan. Patients with clinical stage IA NSCLC (tumour diameter ≤2 cm; consolidation-to-tumour ratio >0·5) were randomly assigned 1:1 to receive either lobectomy or segmentectomy. Randomisation was done via the minimisation method, with balancing for the institution, histological type, sex, age, and thin-section CT findings. Treatment allocation was not concealed from investigators and patients. The primary endpoint was overall survival for all randomly assigned patients. The secondary endpoints were postoperative respiratory function (6 months and 12 months), relapse-free survival, proportion of local relapse, adverse events, proportion of segmentectomy completion, duration of hospital stay, duration of chest tube placement, duration of surgery, amount of blood loss, and the number of automatic surgical staples used. Overall survival was analysed on an intention-to-treat basis with a non-inferiority margin of 1·54 for the upper limit of the 95% CI of the hazard ratio (HR) and estimated using a stratified Cox regression model. This study is registered with UMIN Clinical Trials Registry, UMIN000002317.

Findings: Between Aug, 10, 2009, and Oct 21, 2014, 1106 patients (intention-to-treat population) were enrolled to receive lobectomy (n=554) or segmentectomy (n=552). Patient baseline clinicopathological factors were well balanced between the groups. In the segmentectomy group, 22 patients were switched to lobectomies and one patient received wide wedge resection. At a median follow-up of 7·3 years (range 0·0–10·9), the 5-year overall survival was 94·3% (92·1–96·0) for segmentectomy and 91·1% for lobectomy (95% CI 88·4–93·2); superiority and non-inferiority in overall survival were confirmed using a stratified Cox regression model (HR 0·663; 95% CI 0·474–0·927; one-sided p<0·0001 for non-inferiority; p=0·0082 for superiority). Improved overall survival was observed consistently across all predefined subgroups in the segmentectomy group. At 1 year follow-up, the significant difference in the reduction of median forced expiratory volume in 1 sec between the two groups was 3·5% (p<0·0001), which did not reach the predefined threshold for clinical significance of 10%. The 5-year relapse-free survival was 88·0% (95% CI 85·0–90·4) for segmentectomy and 87·9% (84·8–90·3) for lobectomy (HR 0·998; 95% CI 0·753–1·323; p=0·9889). The proportions of patients with local relapse were 10·5% for segmentectomy and 5·4% for lobectomy (p=0·0018). 52 (63%) of 83 patients and 27 (47%) of 58 patients died of other diseases after lobectomy and segmentectomy, respectively. No 30-day or 90-day mortality was observed. One or more postoperative complications of grade 2 or worse occurred at similar

frequencies in both groups (142 [26%] patients who received lobectomy, 148 [27%] who received segmentectomy).

Interpretation: To our knowledge, this study was the first phase 3 trial to show the benefits of segmentectomy versus lobectomy in overall survival of patients with small-peripheral NSCLC. The findings suggest that segmentectomy should be the standard surgical procedure for this population of patients.

Funding: National Cancer Center Research and the Ministry of Health, Labour, and Welfare of Japan.

Tonorezos Emily S, Cohn Richard J, Glaser Adam W, Lewin Jeremy, Oeffinger Kevin C. Long-term care for people treated for cancer during childhood and adolescence. *Lancet 2022;* 399(10334): 1561-72p.

Abstract:

Worldwide advances in treatment and supportive care for children and adolescents with cancer have resulted in a increasing population of survivors growing into adulthood. Yet, this population is at very high risk of late occurring health problems, including significant morbidity and early mortality. Unique barriers to high-quality care for this group include knowledge gaps among both providers and survivors as well as fragmented health-care delivery during the transition from paediatric to adult care settings. Survivors of childhood and adolescent cancer are at risk for a range of late-occuring side-effects from treatment, including cardiac, endocrine, pulmonary, fertility, renal, psychological, cognitive, and socio-developmental impairments. Care coordination and transition to adult care are substantial challenges, but can be empowering for survivors and improve outcomes, and could be facilitated by clear, effective communication and support for self-management. Resources for adult clinical care teams and primary care providers include late-effects surveillance guidelines and web-based support services.

Variation in the COVID-19 infection–fatality ratio by age, time, and geography during the pre-vaccine era: A systematic analysis. *Lancet 2022;* 399(10334): 1469-88p.

Abstract:

Background: The infection–fatality ratio (IFR) is a metric that quantifies the likelihood of an individual dying once infected with a pathogen. Understanding the determinants of IFR variation for COVID-19, the disease caused by the SARS-CoV-2 virus, has direct implications for mitigation efforts with respect to clinical practice, non-pharmaceutical interventions, and the prioritisation of risk groups for targeted vaccine delivery. The IFR is also a crucial parameter in COVID-19 dynamic transmission models, providing a way to convert a population's mortality rate into an estimate of infections.

Methods: We estimated age-specific and all-age IFR by matching seroprevalence surveys to total COVID-19 mortality rates in a population. The term total COVID-19 mortality refers to an estimate of the total number of deaths directly attributable to COVID-19. After applying exclusion criteria to 5131 seroprevalence surveys, the IFR analyses were informed by 2073 all-age surveys and 718 age-specific surveys (3012 age-specific observations). When seroprevalence was reported by age group, we split total COVID-19 mortality into corresponding age groups using a Bayesian hierarchical model to characterise the non-linear age pattern of reported deaths for a given location. To remove the impact of vaccines on the estimated IFR age pattern, we excluded age-specific observations of seroprevalence and deaths that occurred after vaccines were introduced in a location. We estimated age-specific IFR with a non-linear meta-regression and used the resulting age pattern to standardise all-age IFR observations to the global age distribution. All IFR observations were adjusted for baseline and waning antibody-test sensitivity. We then modelled age-standardised IFR as a function of time, geography, and an ensemble of 100 of the top-performing covariate sets. The covariates included seven clinical predictors (eg, age-standardised obesity prevalence) and two measures of health system performance. Final estimates for 190 countries and territories, as well as subnational locations in 11 countries and territories, were obtained by predicting age-standardised IFR conditional on covariates and reversing the age standardisation.

Findings: We report IFR estimates for April 15, 2020, to January 1, 2021, the period before the introduction of vaccines and widespread evolution of variants. We found substantial heterogeneity in the IFR by age, location, and time. Age-specific IFR estimates form a J shape, with the lowest IFR occurring at age 7 years (0·0023%, 95% uncertainty interval [UI] 0·0015–0·0039) and increasing exponentially through ages 30 years (0·0573%, 0·0418–0·0870), 60 years (1·0035%, 0·7002–1·5727), and 90 years (20·3292%, 14·6888–28·9754). The countries with the highest IFR on July 15, 2020, were Portugal (2·085%, 0·946–4·395), Monaco (1·778%, 1·265–2·915), Japan (1·750%, 1·302–2·690), Spain (1·710%, 0·991–2·718), and Greece (1·637%, 1·155–2·678). All-age IFR varied by a factor of more than 30 among 190 countries and territories. After age standardisation, the countries with the highest IFR on July 15, 2020, were Peru (0·911%, 0·636–1·538), Portugal (0·850%, 0·386–1·793), Oman (0·762%, 0·381–1·399), Spain (0·751%, 0·435–1·193), and Mexico (0·717%, 0·426–1·404). Subnational locations with high IFRs also included hotspots in the UK and southern and eastern states of the USA. Sub-Saharan African countries and Asian countries generally had the lowest all-age and age-standardised IFRs. Population age structure accounted for 74% of logit-scale variation in IFRs estimated for 39 in-sample countries on July 15, 2020. A post-hoc analysis showed that high rates of transmission in the care home population might account for higher IFRs in some locations. Among all countries and territories, we found that the median IFR decreased from 0·466% (interquartile range 0·223–0·840) to 0·314% (0·143–0·551) between April 15, 2020, and Jan 1, 2021.

Interpretation: Estimating the IFR for global populations helps to identify relative vulnerabilities to COVID-19. Information about how IFR varies by age, time, and location informs clinical practice and non-pharmaceutical interventions like physical distancing measures, and underpins vaccine risk stratification. IFR and mortality risk form a J shape with respect to age, which previous research, such as that by Glynn and Moss in 2020, has identified to be a common pattern among infectious diseases. Understanding the experience of a population with COVID-19 mortality requires consideration for local factors; IFRs varied by a factor of more than 30 among 190 countries and territories in this analysis. In particular, the presence of elevated age-standardised IFRs in countries with well resourced health-care systems indicates that factors beyond health-care capacity are important. Potential extenuating circumstances include outbreaks among care home residents, variable burdens of severe cases, and the population prevalence of comorbid conditions that increase the severity of COVID-19 disease. During the pre-vaccine period, the estimated 33% decrease in median IFR over 8 months suggests that treatment for COVID-19 has improved over time. Estimating IFR for the pre-vaccine era provides an important baseline for describing the progression of COVID-19 mortality patterns.

Funding: Bill & Melinda Gates Foundation, J Stanton, T Gillespie, and J and E Nordstrom.

Wang Haidong, Paulson Katherine R, Pease Spencer A, Watson Stefanie, Murray Christopher JL. Estimating excess mortality due to the COVID-19 pandemic: A systematic analysis of COVID-19-related mortality, 2020–21. *Lancet 2022;* 399(10334): 1513-36p.

Abstract:

Background: Mortality statistics are fundamental to public health decision making. Mortality varies by time and location, and its measurement is affected by well known biases that have been exacerbated during the COVID-19 pandemic. This paper aims to estimate excess mortality from the COVID-19 pandemic in 191 countries and territories, and 252 subnational units for selected countries, from Jan 1, 2020, to Dec 31, 2021.

Methods: All-cause mortality reports were collected for 74 countries and territories and 266 subnational locations (including 31 locations in low-income and middle-income countries) that had reported either weekly or monthly deaths from all causes during the pandemic in 2020 and 2021, and for up to 11 year previously. In addition, we obtained excess mortality data for 12 states in India. Excess mortality over time was calculated as observed mortality, after excluding data from periods affected by late registration and anomalies such as heat waves, minus expected mortality. Six models were used to estimate expected mortality; final estimates of expected mortality were based on an ensemble of these models. Ensemble weights were based on root mean squared errors derived from an out-of-

sample predictive validity test. As mortality records are incomplete worldwide, we built a statistical model that predicted the excess mortality rate for locations and periods where all-cause mortality data were not available. We used least absolute shrinkage and selection operator (LASSO) regression as a variable selection mechanism and selected 15 covariates, including both covariates pertaining to the COVID-19 pandemic, such as seroprevalence, and to background population health metrics, such as the Healthcare Access and Quality Index, with direction of effects on excess mortality concordant with a meta-analysis by the US Centers for Disease Control and Prevention. With the selected best model, we ran a prediction process using 100 draws for each covariate and 100 draws of estimated coefficients and residuals, estimated from the regressions run at the draw level using draw-level input data on both excess mortality and covariates. Mean values and 95% uncertainty intervals were then generated at national, regional, and global levels. Out-of-sample predictive validity testing was done on the basis of our final model specification.

Findings: Although reported COVID-19 deaths between Jan 1, 2020, and Dec 31, 2021, totalled 5·94 million worldwide, we estimate that 18·2 million (95% uncertainty interval 17·1–19·6) people died worldwide because of the COVID-19 pandemic (as measured by excess mortality) over that period. The global all-age rate of excess mortality due to the COVID-19 pandemic was 120·3 deaths (113·1–129·3) per 100 000 of the population, and excess mortality rate exceeded 300 deaths per 100 000 of the population in 21 countries. The number of excess deaths due to COVID-19 was largest in the regions of south Asia, north Africa and the Middle East, and eastern Europe. At the country level, the highest numbers of cumulative excess deaths due to COVID-19 were estimated in India (4·07 million [3·71–4·36]), the USA (1·13 million [1·08–1·18]), Russia (1·07 million [1·06–1·08]), Mexico (798 000 [741 000–867 000]), Brazil (792 000 [730 000–847 000]), Indonesia (736 000 [594 000–955 000]), and Pakistan (664 000 [498 000–847 000]). Among these countries, the excess mortality rate was highest in Russia (374·6 deaths [369·7–378·4] per 100 000) and Mexico (325·1 [301·6–353·3] per 100 000), and was similar in Brazil (186·9 [172·2–199·8] per 100 000) and the USA (179·3 [170·7–187·5] per 100 000).

Interpretation: The full impact of the pandemic has been much greater than what is indicated by reported deaths due to COVID-19 alone. Strengthening death registration systems around the world, long understood to be crucial to global public health strategy, is necessary for improved monitoring of this pandemic and future pandemics. In addition, further research is warranted to help distinguish the proportion of excess mortality that was directly caused by SARS-CoV-2 infection and the changes in causes of death as an indirect consequence of the pandemic.

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Abstract:

Rubella is an acute illness caused by rubella virus and characterised by fever and rash. Although rubella is a clinically mild illness, primary rubella virus infection in early pregnancy can result in congenital rubella syndrome, which has serious medical and public health consequences. WHO estimates that approximately 100 000 congenital rubella syndrome cases occur per year. Rubella virus is transmitted through respiratory droplets and direct contact. 25–50% of people infected with rubella virus are asymptomatic. Clinical disease often results in mild, self-limited illness characterised by fever, a generalised erythematous maculopapular rash, and lymphadenopathy. Complications include arthralgia, arthritis, thrombocytopenic purpura, and encephalitis. Common presenting signs and symptoms of congenital rubella syndrome include cataracts, sensorineural hearing impairment, congenital heart disease, jaundice, purpura, hepatosplenomegaly, and microcephaly. Rubella and congenital rubella syndrome can be prevented by rubella-containing vaccines, which are commonly administered in combination with measles vaccine. Although global rubella vaccine coverage reached only 70% in 2020 global rubella eradiation remains an ambitious but achievable goal.

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