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NRF2 and Thioredoxin Reductase 1 as Modulators of Interactions between Zinc and Selenium.

Löser A, Schwarz M, Kipp AP.

Background: Selenium and zinc are essential trace elements known to regulate cellular processes including redox homeostasis. During inflammation, circulating selenium and zinc concentrations are reduced in parallel, but underlying mechanisms are unknown. Accordingly, we modulated the zinc and selenium supply of HepG2 cells to study their relationship. Methods: HepG2 cells were supplied with selenite in combination with a short- or long-term zinc treatment to investigate intracellular concentrations of selenium and zinc together with biomarkers describing their status. In addition, the activation of the redox-sensitive transcription factor NRF2 was analyzed. Results: Zinc not only increased the nuclear translocation of NRF2 after 2 to 6 h but also enhanced the intracellular selenium content after 72 h, when the cells were exposed to both trace elements. In parallel, the activity and expression of the selenoprotein thioredoxin reductase 1 (TXNRD1) increased, while the gene expression of other selenoproteins remained unaffected or was even downregulated. The zinc effects on the selenium concentration and TXNRD activity were reduced in cells with stable NRF2 knockdown in comparison to control cells. Conclusions: This indicates a functional role of NRF2 in mediating the zinc/selenium crosstalk and provides an explanation for the observed unidirectional behavior of selenium and zinc.

Transcriptomics pave the way into mechanisms of cobalt and nickel toxicity: Nrf2-mediated cellular responses in liver carcinoma cells.

Thiel A, Drews F, Pirritano M, Schumacher F, Michaelis V, Schwarz M, Franzenburg S, Schwerdtle T, Michalke B, Kipp AP, Kleuser B, Simon M, Bornhorst J.

Cobalt (Co) and Nickel (Ni) are used nowadays in various industrial applications like lithium-ion batteries, raising concerns about their environmental release and public health threats. Both metals are potentially carcinogenic and may cause neurological and cardiovascular dysfunctions, though underlying toxicity mechanisms have to be further elucidated. This study employs untargeted transcriptomics to analyze downstream cellular effects of individual and combined Co and Ni toxicity in human liver carcinoma cells (HepG2). The results reveal a synergistic effect of Co and Ni, leading to significantly higher number of differentially expressed genes (DEGs) compared to individual exposure. There was a clear enrichment of Nrf2 regulated genes linked to pathways such as glycolysis, iron and glutathione metabolism, and sphingolipid metabolism, confirmed by targeted analysis. Co and Ni exposure alone and combined caused nuclear Nrf2 translocation, while only combined exposure significantly affects iron and glutathione metabolism, evidenced by upregulation of HMOX-1 and iron storage protein FTL. Both metals impact sphingolipid metabolism, increasing dihydroceramide levels and decreasing ceramides, sphingosine and lactosylceramides, along with diacylglycerol accumulation. By combining transcriptomics and analytical methods, this study provides valuable insights into molecular mechanisms of Co and Ni toxicity, paving the way for further understanding of metal stress.

Source of Vitamin B12 in plants of the Lemnaceae family and its production by duckweed-associated bacteria

Kenneth A, Sowjanya Sree K, Okamoto N, Koseki K, Sorrels S, Jahreis G, Watanabe F, Appenroth K-J, Lam E.

Variable vitamin B12 content was found in 15 unsterile duckweed (Lemnaceae) clones. Lower microbial content in duckweeds, validated by PCR methods, correlated with low vitamin B12. Two strains of duckweed-associated bacteria are vitamin B12 producers. Our results provide evidence for the bacterial origin of vitamin B12 in duckweeds. Fortifying duckweeds with B12-producing endophytes may contribute to a Planetary Healthy Diet.

Duckweed should and can contribute to human nutrition in the future

Appenroth K-J, Jahreis G, Sowjanya Sree K.

The nutritional composition of duckweed in relation to human food was extensively investigated in its genera. It has been shown that under optimal cultivation conditions the protein content is high but fat and starch contents are low. Under stressed conditions, the starch content of these plants dramatically increases and the protein content decreases in parallel. This is not desirable for use as human food in the present scenario. Thus, optimal cultivation conditions are required for production of duckweed as human food.
The trend towards vegan diets in industrial societies leads to a deficiency of several nutrients. First and foremost, there is an increased risk of vitamin B12 deficiency if vegans do not take appropriate supplements. B12 deficiency can lead to neurological disorders. Plant foods contain little or no vitamin B12. A selection of suitable clones of duckweed and effective B12 producers therefore represents an opportunity to create special plant-based products that can accepted by vegans and can significantly improve their health status. Bioinformatics-aided identification of vitamin B12 producers among duckweed-associated bacteria could facilitate their systematic incorporation into duckweed-based foods to support a planetary health diet. Fresh plants of W. arrhiza and W. globosa (EFSA, European Food Safety Authority, 2021) and protein extracts of Lemna gibba and L. minor (EFSA Panel on Nutrition, Novel Foods and Food Allergens, 2023) were recognised by the European Food Safety Authority as novel food to be "safe under the conditions of use".

Potenziell kritische Nährstoffe bei vegetarischer und veganer Ernährung, Empfehlungen zur bedarfsgerechten Zufuhr – Teil 2,

Dawczynski C.

Pflanzliche Lebensmittel bieten ein vielfältiges Spektrum an nährstoffreichen Lebensmitteln. Dennoch kann der Verzicht auf einzelne Lebensmittel oder Lebensmittelgruppen dazu führen, dass essenzielle Nährstoffe nicht in bedarfsgerechten Mengen zugeführt werden. Dies kann langfristig die Ausbildung von Nährstoffmangelerscheinungen begünstigen. Der vorliegende Beitrag ist der zweite Teil der Betrachtung kritischer Nährstoffe vegetarischer und veganer Ernährungsweisen. Neben Informationen zu den physiologischen Wirkungen und Zufuhrempfehlungen sind Angaben zur aktuellen Versorgungslage sowie Möglichkeiten zur Bedarfsdeckung und geeignete Laborparameter bzw. Untersuchungsmethoden enthalten. Im ersten Teil wurden bereits Protein und unentbehrliche Aminosäuren, langkettige n-3-Fettsäuren sowie die Vitamine B12, B2 und A vorgestellt. Der Fokus des zweiten Teils liegt auf Mineralstoffen und Spurenelementen, genauer Calcium, Eisen, Zink, Selen und Jod.

Kritische Nährstoffe bei veganer Ernährung: alte Bekannte und neue Verdächtige.
Dawczynski C.

KERNAUSSAGEN (Artikel enthält kein Abstract)
- Eine einseitige Lebensmittelauswahl geht in jeder Ernährungsform damit einher, dass essenzielle Nährstoff e nicht bedarfsgerecht aufgenommen werden.
- Zu den kritischen Nährstoff en in der veganen Ernährung gehören Protein und essenzielle AS, n-3-LC-PUFA, Vitamin A, Vitamin B2, Vitamin B 12, Calcium, Eisen, Zink, Jod und Selen. Bis auf Vitamin B 12 können diese durch pflanzliche Lebensmittel aufgenommen werden.
- Um eine bedarfsgerechte Zufuhr sicherzustellen, sollten die verfügbaren pflanzlichen Quellen miteinander kombiniert werden.
- Es ist wichtig, das komplette Spektrum der zur Verfügung stehenden pflanzlichen Lebensmittel zu nutzen.

Bioactive compounds and antioxidant capacity of pulp, peel and seeds from jeriva (Syagrus romanzoffiana)
Mello B, Malarski A, Böhm V.

Jeriva (Syagrus romanzoffiana) is a fruit from palm trees of the Arecaceae family, widely distributed in tropical and subtropical areas of Latin America. It has low production costs and high productivity throughout the year; however, its consumption is very low, and the production goes almost entirely to feed animals or to waste. To improve its consumption, a good characterization of the whole fruit is necessary. The objective of this work was to evaluate the jeriva pulp, peel and seeds according to carotenoids, phenolic compounds, vitamin C, tocopherols and antioxidant potential using HPLC, microplate readers and spectrophotometric methods. Every part of the fruit exhibited antioxidant capacity in the ORAC and TEAC tests, which can be attributed to its high concentration of polyphenols. Carotenoids were more present in the pulp and peel and almost absent in the seeds. Vitamin C ranged from 12 ± 1 for the seeds up to 92 ± 3 mg/100 g for the pulp. The total phenolic content was quantified between 473 ± 39 for the seeds and 1089 ± 32 mg of gallic acid equivalents (GAEs)/100 g for the pulp. These results demonstrate that all parts of this fruit have important bioactive nutrients, with promising perspectives for further scientific approaches and for composing formulations of food products to enhance functional properties.

Associations between serum mineral concentrations and mortality by renal function in the Ludwigshafen Risk and Cardiovascular Health Study.

Moissl AP, Delgado GE, Kleber ME, Krämer BK, März W, Lorkowski S.

The association of serum concentrations of minerals and phosphate with overall and cardiovascular mortality based on renal function is poorly understood. 3307 patients (average age 62.7 ± 10.6 years) in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study were grouped by estimated glomerular filtration rate (eGFR) into three categories: < 60, 60-89, and ≥ 90 mL/min per 1.73 m2, per KDIGO 2022 guidelines and were analysed using Cox regression. Low serum sodium and iron concentrations were associated with poor renal function and increased overall mortality risk, whereas higher serum zinc concentrations were associated with reduced overall and cardiovascular mortality risk. Elevated serum copper concentrations were associated with increased mortality risk across all eGFR categories. Comparing low and normal eGFR, we observed a fourfold increase in all-cause mortality risk for eGFR < 60 mL/min per 1.73 m2 and a twofold increase for eGFR 60-89 mL/min per 1.73 m2, accompanied by changes in serum mineral concentrations. The optimal range of mineral and phosphate concentrations in serum was strongly related to renal function. To reduce mortality risk, it's important to regularly monitor serum mineral and phosphate concentrations as well as renal function, especially in cardiovascular patients with compromised renal function.

α-Tocopherol long-chain metabolite α-T-13'-COOH exhibits biphasic effects on cell viability, induces ROS-dependent DNA damage, and modulates redox status in murine RAW264.7 macrophages.

Liao S, Börmel L, Müller AK, Gottschalk L, Pritsch N, Preisner LZ, Samokhina O, Schwarz M, Kipp AP, Schlörmann W, Glei M, Schubert M, Schmölz L, Wallert M, Lorkowski S.

Scope: The α-tocopherol long-chain metabolite α-tocopherol-13'-hydroxy-chromanol (α-T-13'-COOH) is a proposed regulatory intermediate of endogenous vitamin E metabolism. Effects of α-T-13'-COOH on cell viability and adaptive stress response are not well understood. The present study aims to investigate the concentration-dependent effects of α-T-13'-COOH on cellular redox homeostasis, genotoxicity, and cytotoxicity in murine RAW264.7 macrophages as a model system.
Methods and Results: Murine RAW264.7 macrophages are exposed to various dosages of α-T-13'-COOH to determine its regulatory effects on reactive oxygen species (ROS) production, DNA damage, expression of stress-related markers, and the activity of ROS scavenging enzymes including superoxide dismutases, catalase, and glutathione-S-transferases. The impact on cell viability is assessed by analyzing cell proliferation, cell cycle arrest, and cell apoptosis.
Conclusion: α-T-13'-COOH influences ROS production and induces DNA damage in a dose-dependent manner. The metabolite modulates the activity of ROS-scavenging enzymes, with significant changes observed in the activities of antioxidant enzymes. A biphasic response affecting cell viability is noted: sub-micromolar doses of α-T-13'-COOH promote cell proliferation and enhance DNA synthesis, whereas supraphysiological doses lead to DNA damage and cytotoxicity. It hypothesizes an adaptive stress response, characterized by upregulation of ROS detoxification mechanisms, enhanced cell cycle arrest, and increased apoptosis, indicating a correlation with oxidative stress and subsequent cellular damage.

Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021.

Background: Up-to-date estimates of stroke burden and attributable risks and their trends at global, regional, and national levels are essential for evidence-based health care, prevention, and resource allocation planning. We aimed to provide such estimates for the period 1990-2021. Methods: We estimated incidence, prevalence, death, and disability-adjusted life-year (DALY) counts and age-standardised rates per 100 000 people per year for overall stroke, ischaemic stroke, intracerebral haemorrhage, and subarachnoid haemorrhage, for 204 countries and territories from 1990 to 2021. We also calculated burden of stroke attributable to 23 risk factors and six risk clusters (air pollution, tobacco smoking, behavioural, dietary, environmental, and metabolic risks) at the global and regional levels (21 GBD regions and Socio-demographic Index [SDI] quintiles), using the standard GBD methodology. 95% uncertainty intervals (UIs) for each individual future estimate were derived from the 2·5th and 97·5th percentiles of distributions generated from
propagating 500 draws through the multistage computational pipeline.
Findings: In 2021, stroke was the third most common GBD level 3 cause of death (7·3 million [95% UI 6·6-7·8] deaths; 10·7% [9·8-11·3] of all deaths) after ischaemic heart disease and COVID-19, and the fourth most common cause of DALYs (160·5 million [147·8-171·6] DALYs; 5·6% [5·0-6·1] of all DALYs). In 2021, there were 93·8 million (89·0-99·3) prevalent and 11·9 million (10·7-13·2) incident strokes. We found disparities in stroke burden and risk factors by GBD region, country or territory, and SDI, as well as a stagnation in the reduction of incidence from 2015 onwards, and even some increases in the stroke incidence, death, prevalence, and DALY rates in southeast Asia, east Asia, and Oceania, countries with lower SDI, and people younger than 70 years. Globally, ischaemic stroke constituted 65·3% (62·4-67·7), intracerebral haemorrhage constituted 28·8% (28·3-28·8), and subarachnoid haemorrhage constituted 5·8% (5·7-6·0) of incident strokes. There were substantial increases in DALYs attributable to high BMI (88·2% [53·4-117·7]), high ambient temperature (72·4% [51·1 to 179·5]), high fasting plasma glucose (32·1% [26·7-38·1]), diet high in sugar-sweetened beverages (23·4% [12·7-35·7]), low physical activity (11·3% [1·8-34·9]), high systolic blood pressure (6·7% [2·5-11·6]), lead exposure (6·5% [4·5-11·2]), and diet low in omega-6 polyunsaturated fatty acids (5·3% [0·5-10·5]).
Interpretation: Stroke burden has increased from 1990 to 2021, and the contribution of several risk factors has also increased. Effective, accessible, and affordable measures to improve stroke surveillance, prevention (with the emphasis on blood pressure, lifestyle, and environmental factors), acute care, and rehabilitation need to be urgently implemented across all countries to reduce stroke burden.

Changing impact of dietary risk factors on cardiovascular mortality in 46 European countries from 1990 to 2019 by age and sex: A data article of the GBD Study.

Pörschmann T, Meier T, Lorkowski S.

This study aimed to estimate the association between single dietary risk factors and cardiovascular mortality in the WHO European Region, its four subregions and 46 individual countries. For this purpose, data from the Global Burden of Diseases Study (GBD) 2019 iteration were employed and analysed according to age (≥ 25 years) and sex. The comparative risk assessment framework of the GBD was utilized in order to estimate the number of cardiovascular deaths that could be attributed to 13 dietary risks. The study period spanned from 1990 to 2019. Between 1990 and 2019 the absolute number of diet-related cardiovascular deaths (DRCDs) in the WHO ER decreased from 1.69 to 1.55 million deaths. Moreover, a decline in the absolute number of deaths was observed in two subregions and 27 countries. In 2019, the number of deaths was almost equally distributed between women and men. This distribution has undergone only slight temporal changes. The number of cases for men were found to be higher in three subregions and in 30 countries. The majority of DRCDs in the WHO ER were attributable to 'a diet low in whole grains', which was also the primary risk factor in three subregions und 29 countries. The next most-common risk factor was 'a diet low in legumes', followed by 'a diet high in sodium'. In particular, the risk factor 'a diet high in sodium' was a significant contributing factor in Central Europe. In addition, the risk factor 'a diet high in red meat' was more pronounced in Western Europe than in the other regions and slightly more influential in the group of women across all regions. For men 'a diet high in sodium' was more prominent than for women. In essence, slight changes in the influence of individual risk factors were observed across the different age groups. The datasheets enable the observation of changes within the dietary risks over time, their distribution by age and sex, and differences between regions and individual countries in detail. This allows for an individual assessment of the problem situation for each country, the subregions and the European Region as a whole, with the aim of developing solution strategies based on this assessment. Dietary interventions can focus on the relevant food and target groups in order to support a health-promoting diet.

Background: The European Union (EU) faces many health-related challenges. Burden of diseases information and the resulting trends over time are essential for health planning. This paper reports estimates of disease burden in the EU and individual 27 EU countries in 2019, and compares them with those in 2010.

Methods: We used the Global Burden of Disease 2019 study estimates and 95% uncertainty intervals for the whole EU and each country to evaluate age-standardised death, years of life lost (YLLs), years lived with disability (YLDs) and disability-adjusted life years (DALYs) rates for Level 2 causes, as well as life expectancy and healthy life expectancy (HALE).

Results: In 2019, the age-standardised death and DALY rates in the EU were 465.8 deaths and 20,251.0 DALYs per 100,000 inhabitants, respectively. Between 2010 and 2019, there were significant decreases in age-standardised death and YLL rates across EU countries. However, YLD rates remained mainly unchanged. The largest decreases in age-standardised DALY rates were observed for "HIV/AIDS and sexually transmitted diseases" and "transport injuries" (each -19%). "Diabetes and kidney diseases" showed a significant increase for age-standardised DALY rates across the EU (3.5%). In addition, "mental disorders" showed an increasing age-standardised YLL rate (14.5%).

Conclusions: There was a clear trend towards improvement in the overall health status of the EU but with differences between countries. EU health policymakers need to address the burden of diseases, paying specific attention to causes such as mental disorders. There are many opportunities for mutual learning among otherwise similar countries with different patterns of disease.

Global burden and strength of evidence for 88 risk factors in 204 countries and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021.

GBD 2021 Risk Factors Collaborators.

Background: Understanding the health consequences associated with exposure to risk factors is necessary to inform public health policy and practice. To systematically quantify the contributions of risk factor exposures to specific health outcomes, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 aims to provide comprehensive estimates of exposure levels, relative health risks, and attributable burden of disease for 88 risk factors in 204 countries and territories and 811 subnational locations, from 1990 to 2021.

Methods: The GBD 2021 risk factor analysis used data from 54 561 total distinct sources to produce epidemiological estimates for 88 risk factors and their associated health outcomes for a total of 631 risk-outcome pairs. Pairs were included on the basis of data-driven determination of a risk-outcome association. Age-sex-location-year-specific estimates were generated at global, regional, and national levels. Our approach followed the comparative risk assessment framework predicated on a causal web of hierarchically organised, potentially combinative, modifiable risks. Relative risks (RRs) of a given outcome occurring as a function of risk factor exposure were estimated separately for each risk-outcome pair, and summary exposure values (SEVs), representing risk-weighted exposure prevalence, and theoretical minimum risk exposure levels (TMRELs) were estimated for each risk factor. These estimates were used to calculate the population attributable fraction (PAF; ie, the proportional change in health risk that would occur if exposure to a risk factor were reduced to the TMREL). The product of PAFs and disease burden associated with a given outcome, measured in disability-adjusted life-years (DALYs), yielded measures of attributable burden (ie, the proportion of total disease burden attributable to a particular risk factor or combination of risk factors). Adjustments for mediation were applied to account for relationships involving risk factors that act indirectly on outcomes via intermediate risks. Attributable burden estimates were stratified by Socio-demographic Index (SDI) quintile and presented as counts, age-standardised rates, and rankings. To complement estimates of RR and attributable burden, newly developed burden of proof risk function (BPRF) methods were applied to yield supplementary, conservative interpretations of risk-outcome associations based on the consistency of underlying evidence, accounting for unexplained heterogeneity between input data from different studies. Estimates reported represent the mean value across 500 draws from the estimate's distribution, with 95% uncertainty intervals (UIs) calculated as the 2·5th and 97·5th percentile values across the draws.

Findings: Among the specific risk factors analysed for this study, particulate matter air pollution was the leading contributor to the global disease burden in 2021, contributing 8·0% (95% UI 6·7-9·4) of total DALYs, followed by high systolic blood pressure (SBP; 7·8% [6·4-9·2]), smoking (5·7% [4·7-6·8]), low birthweight and short gestation (5·6% [4·8-6·3]), and high fasting plasma glucose (FPG; 5·4% [4·8-6·0]). For younger demographics (ie, those aged 0-4 years and 5-14 years), risks such as low birthweight and short gestation and unsafe water, sanitation, and handwashing (WaSH) were among the leading risk factors, while for older age groups, metabolic risks such as high SBP, high body-mass index (BMI), high FPG, and high LDL cholesterol had a greater impact. From 2000 to 2021, there was an observable shift in global health challenges, marked by a decline in the number of all-age DALYs broadly attributable to behavioural risks (decrease of 20·7% [13·9-27·7]) and environmental and occupational risks (decrease of 22·0% [15·5-28·8]), coupled with a 49·4% (42·3-56·9) increase in DALYs attributable to metabolic risks, all reflecting ageing populations and changing lifestyles on a global scale. Age-standardised global DALY rates attributable to high BMI and high FPG rose considerably (15·7% [9·9-21·7] for high BMI and 7·9% [3·3-12·9] for high FPG) over this period, with exposure to these risks increasing annually at rates of 1·8% (1·6-1·9) for high BMI and 1·3% (1·1-1·5) for high FPG. By contrast, the global risk-attributable

burden and exposure to many other risk factors declined, notably for risks such as child growth failure and unsafe water source, with age-standardised attributable DALYs decreasing by 71·5% (64·4-78·8) for child growth failure and 66·3% (60·2-72·0) for unsafe water source. We separated risk factors into three groups according to trajectory over time: those with a decreasing attributable burden, due largely to declining risk exposure (eg, diet high in trans-fat and household air pollution) but also to proportionally smaller child and youth populations (eg, child and maternal malnutrition); those for which the burden increased moderately in spite of declining risk exposure, due largely to population ageing (eg, smoking); and those for which the burden increased considerably due to both increasing risk exposure and population ageing (eg, ambient particulate matter air pollution, high BMI, high FPG, and high SBP).

Interpretation: Substantial progress has been made in reducing the global disease burden attributable to a range of risk factors, particularly those related to maternal and child health, WaSH, and household air pollution. Maintaining efforts to minimise the impact of these risk factors, especially in low SDI locations, is necessary to sustain progress. Successes in moderating the smoking-related burden by reducing risk exposure highlight the need to advance policies that reduce exposure to other leading risk factors such as ambient particulate matter air pollution and high SBP. Troubling increases in high FPG, high BMI, and other risk factors related to obesity and metabolic syndrome indicate an urgent need to identify and implement interventions.

Protein intake and cancer: an umbrella review of systematic reviews for the evidence-based guideline of the German Nutrition Society.

Kühn T, Kalotai N, Amini AM, Haardt J, Lehmann A, Schmidt A, Buyken AE, Egert S, Ellinger S, Kroke A, Lorkowski S, Louis S, Schulze MB, Schwingshackl L, Siener R, Stangl GI, Watzl B, Zittermann A, Nimptsch K; German Nutrition Society.

Purpose: It has been proposed that a higher habitual protein intake may increase cancer risk, possibly via upregulated insulin-like growth factor signalling. Since a systematic evaluation of human studies on protein intake and cancer risk based on a standardised assessment of systematic reviews (SRs) is lacking, we carried out an umbrella review of SRs on protein intake in relation to risks of different types of cancer.

Methods: Following a pre-specified protocol (PROSPERO: CRD42018082395), we retrieved SRs on protein intake and cancer risk published before January 22th 2024, and assessed the methodological quality and outcome-specific certainty of the evidence using a modified version of AMSTAR 2 and NutriGrade, respectively. The overall certainty of evidence was rated according to predefined criteria.

Results: Ten SRs were identified, of which eight included meta-analyses. Higher total protein intake was not associated with risks of breast, prostate, colorectal, ovarian, or pancreatic cancer incidence. The methodological quality of the included SRs ranged from critically low (kidney cancer), low (pancreatic, ovarian and prostate cancer) and moderate (breast and prostate cancer) to high (colorectal cancer). The outcome-specific certainty of the evidence underlying the reported findings on protein intake and cancer risk ranged from very low (pancreatic, ovarian and prostate cancer) to low (colorectal, ovarian, prostate, and breast cancer). Animal and plant protein intakes were not associated with cancer risks either at a low (breast and prostate cancer) or very low (pancreatic and prostate cancer) outcome-specific certainty of the evidence. Overall, the evidence for the lack of an association between protein intake and (i) colorectal cancer risk and (ii) breast cancer risk was rated as possible. By contrast, the evidence underlying the other reported results was rated as insufficient.

Conclusion: The present findings suggest that higher total protein intake may not be associated with the risk of colorectal and breast cancer, while conclusions on protein intake in relation to risks of other types of cancer are restricted due to insufficient evidence.

Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021.

GBD 2021 Causes of Death Collaborators.

Background: Regular, detailed reporting on population health by underlying cause of death is fundamental for public health decision making. Cause-specific estimates of mortality and the subsequent effects on life expectancy worldwide are valuable metrics to gauge progress in reducing mortality rates. These estimates are particularly important following large-scale mortality spikes, such as the COVID-19 pandemic. When systematically analysed, mortality rates and life expectancy allow comparisons of the consequences of causes of death globally and over time, providing a nuanced understanding of the effect of these causes on global populations.

Methods: The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021 cause-of-death analysis estimated mortality and years of life lost (YLLs) from 288 causes of death by age-sex-location-year in 204 countries and territories and 811 subnational locations for each year from 1990 until 2021. The analysis used 56 604 data sources, including data from vital registration and verbal autopsy as well as surveys, censuses, surveillance systems, and cancer registries, among others. As with previous GBD rounds, cause-specific death rates for most causes were estimated using the Cause of Death Ensemble model-a modelling tool developed for GBD to assess the out-of-sample predictive validity of different statistical models and covariate permutations and combine those results to produce cause-specific mortality estimates-with alternative strategies adapted to model causes with insufficient data, substantial changes in reporting over the study period, or unusual epidemiology. YLLs were computed as the product of the number of deaths for each cause-age-sex-location-year and the standard life expectancy at each age. As part of the modelling process, uncertainty intervals (UIs) were generated using the 2·5th and 97·5th percentiles from a 1000-draw distribution for each metric. We decomposed life expectancy by cause of death, location, and year to show cause-specific effects on life expectancy from 1990 to 2021. We also used the coefficient of variation and the fraction of population affected by 90% of deaths to highlight concentrations of mortality. Findings are reported in counts and age-standardised rates. Methodological improvements for cause-of-death estimates in GBD 2021 include the expansion of under-5-years age group to include four new age groups, enhanced methods to account for stochastic variation of sparse data, and the inclusion of COVID-19 and other pandemic-related mortality-which includes excess mortality associated with the pandemic, excluding COVID-19, lower respiratory infections, measles, malaria, and pertussis. For this analysis, 199 new country-years of vital registration cause-of-death data, 5 country-years of surveillance data, 21 country-years of verbal autopsy data, and 94 country-years of other data types were added to those used in previous GBD rounds.

Findings: The leading causes of age-standardised deaths globally were the same in 2019 as they were in 1990; in descending order, these were, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, and lower respiratory infections. In 2021, however, COVID-19 replaced stroke as the second-leading age-standardised cause of death, with 94·0 deaths (95% UI 89·2-100·0) per 100 000 population. The COVID-19 pandemic shifted the rankings of the leading five causes, lowering stroke to the third-leading and chronic obstructive pulmonary disease to the fourth-leading position. In 2021, the highest age-standardised death rates from COVID-19 occurred in sub-Saharan Africa (271·0 deaths [250·1-290·7] per 100 000 population) and Latin America and the Caribbean (195·4 deaths [182·1-211·4] per 100 000 population). The lowest age-standardised death rates from COVID-19 were in the high-income super-region (48·1 deaths [47·4-48·8] per 100 000 population) and southeast Asia, east Asia, and Oceania (23·2 deaths [16·3-37·2] per 100 000 population). Globally, life expectancy steadily improved between 1990 and 2019 for 18 of the 22 investigated causes. Decomposition

of global and regional life expectancy showed the positive effect that reductions in deaths from enteric infections, lower respiratory infections, stroke, and neonatal deaths, among others have contributed to improved survival over the study period. However, a net reduction of 1·6 years occurred in global life expectancy between 2019 and 2021, primarily due to increased death rates from COVID-19 and other pandemic-related mortality. Life expectancy was highly variable between super-regions over the study period, with southeast Asia, east Asia, and Oceania gaining 8·3 years (6·7-9·9) overall, while having the smallest reduction in life expectancy due to COVID-19 (0·4 years). The largest reduction in life expectancy due to COVID-19 occurred in Latin America and the Caribbean (3·6 years). Additionally, 53 of the 288 causes of death were highly concentrated in locations with less than 50% of the global population as of 2021, and these causes of death became progressively more concentrated since 1990, when only 44 causes showed this pattern. The concentration phenomenon is discussed heuristically with respect to enteric and lower respiratory infections, malaria, HIV/AIDS, neonatal disorders, tuberculosis, and measles.

Interpretation: Long-standing gains in life expectancy and reductions in many of the leading causes of death have been disrupted by the COVID-19 pandemic, the adverse effects of which were spread unevenly among populations. Despite the pandemic, there has been continued progress in combatting several notable causes of death, leading to improved global life expectancy over the study period. Each of the seven GBD super-regions showed an overall improvement from 1990 and 2021, obscuring the negative effect in the years of the pandemic. Additionally, our findings regarding regional variation in causes of death driving increases in life expectancy hold clear policy utility. Analyses of shifting mortality trends reveal that several causes, once widespread globally, are now increasingly concentrated geographically. These changes in mortality concentration, alongside further investigation of changing risks, interventions, and relevant policy, present an important opportunity to deepen our understanding of mortality-reduction strategies. Examining patterns in mortality concentration might reveal areas where successful public health interventions have been implemented. Translating these successes to locations where certain causes of death remain entrenched can inform policies that work to improve life expectancy for people everywhere.

Dietary protein and blood pressure: an umbrella review of systematic reviews and evaluation of the evidence.

Boeing H, Amini AM, Haardt J, Schmidt A, Bischoff-Ferrari HA, Buyken AE, Egert S, Ellinger S, Kroke A, Lorkowski S, Louis S, Nimptsch K, Schulze MB, Schutkowski A, Schwingshackl L, Siener R, Zittermann A, Watzl B, Stangl GI; German Nutrition Society.

Introduction: This umbrella review aimed to investigate the evidence of an effect of dietary intake of total protein, animal and plant protein on blood pressure (BP), and hypertension (PROSPERO: CRD42018082395).

Methods: PubMed, Embase and Cochrane Database were systematically searched for systematic reviews (SRs) of prospective studies with or without meta-analysis published between 05/2007 and 10/2022. The methodological quality and outcome-specific certainty of evidence were assessed by the AMSTAR 2 and NutriGrade tools, followed by an assessment of the overall certainty of evidence. SRs investigating specific protein sources are described in this review, but not included in the assessment of the overall certainty of evidence.

Results: Sixteen SRs were considered eligible for the umbrella review. Ten of the SRs investigated total protein intake, six animal protein, six plant protein and four animal vs. plant protein. The majority of the SRs reported no associations or effects of total, animal and plant protein on BP (all "possible" evidence), whereby the uncertainty regarding the effects on BP was particularly high for plant protein. Two SRs addressing milk-derived protein showed a reduction in BP; in contrast, SRs investigating soy protein found no effect on BP. The outcome-specific certainty of evidence of the SRs was mostly rated as low.

Discussion/Conclusion: This umbrella review showed uncertainties whether there are any effects on BP from the intake of total protein, or animal or plant proteins, specifically. Based on data from two SRs with milk protein, it cannot be excluded that certain types of protein could favourably influence BP.

Monogenic hypertriglyceridemia and recurrent pancreatitis in a homozygous carrier of a rare APOA5 mutation: a case report.

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Background: Homozygous mutations in the APOA5 gene constitute a rare cause of monogenic hypertriglyceridemia, or familial chylomicronemia syndrome (FCS). We searched PubMed and identified 16 cases of homozygous mutations in the APOA5 gene. Severe hypertriglyceridemia related to monogenic mutations in triglyceride-regulating genes can cause recurrent acute pancreatitis. Standard therapeutic approaches for managing this condition typically include dietary interventions, fibrates, and omega-3-fatty acids. A novel therapeutic approach, antisense oligonucleotide volanesorsen is approved for use in patients with FCS.

Case Presentation: We report a case of a 25-years old Afghani male presenting with acute pancreatitis due to severe hypertriglyceridemia up to 29.8 mmol/L caused by homozygosity in APOA5 (c.427delC, p.Arg143Alafs*57). A low-fat diet enriched with medium-chain TG (MCT) oil and fibrate therapy did not prevent recurrent relapses, and volanesorsen was initiated. Volanesorsen resulted in almost normalized triglyceride levels. No further relapses of acute pancreatitis occurred. Patient reported an improve life quality due to alleviated chronic abdominal pain and headaches.

Conclusions: Our case reports a rare yet potentially life-threatening condition-monogenic hypertriglyceridemia-induced acute pancreatitis. The implementation of the antisense drug volanesorsen resulted in improved triglyceride levels, alleviated symptoms, and enhanced the quality of life.