Neues aus der Wissenschaft

Wissenschaftliche Publikationen aus dem Institut für Ernährungswissenschaften der Friedrich-Schiller-Universität Jena veröffentlich von November 2021 bis April 2022

Use of the ß-Glucan-Producing Lactic Acid Bacteria Strains *Levilactobacillus brevis* and *Pediococcus claussenii* for Sourdough Fermentation - Chemical Characterization and Chemopreventive Potential of In Situ-Enriched Wheat and Rye Sourdoughs and Breads.

Schlörmann W, Bockwoldt JA, Hübner SM, Wittwer E, Reiners S, Lorkowski S, Dawczynski C, Ehrmann MA, Glei M.
Nutrients **2022**, 14, 1510.

The aim of the present study was to examine β-glucan production and the potential prebiotic and chemopreventive effects of wheat and rye sourdoughs and breads generated with wild-type and non-β-glucan-forming isogenic mutant strains of *Levilactobacillus brevis* and *Pediococcus claussenii*. Sourdough and bread samples were subjected to in vitro digestion and fermentation. Fermentation supernatants (FS) and pellets (FP) were analyzed (pH values, short-chain fatty acids (SCFA), ammonia, bacterial taxa) and the effects of FS on LT97 colon adenoma cell growth, viability, caspase-2 and -3 activity, genotoxic and antigenotoxic effects and on gene and protein expression of *p21*, *cyclin D2*, *catalase* and *superoxide dismutase 2* (*SOD2*) were examined. Concentrations of SCFA were increased and concentrations of ammonia were partly reduced in the FS. The relative abundance of Bifidobacteriaceae was increased in all FPs. Treatment with FS reduced the growth and viability of LT97 cells and significantly increased caspase-2 and -3 activities without exhibiting genotoxic or antigenotoxic effects. The *p21* mRNA and protein levels were increased while that of *cyclin D2* was reduced. *Catalase* and *SOD2* mRNA and protein expression were marginally induced. The presented results indicate a comparable chemopreventive potential of wheat and rye sourdoughs and breads without an additional effect of the formed β-glucan.

Artificial Digestion of Polydisperse Copper Oxide Nanoparticles: Investigation of Effects on the Human In Vitro Intestinal Co-Culture Model Caco-2/HT29-MTX.

Büttner J, Schneider T, Westermann M, Glei M.
Toxics **2022**, 10, 130.

Copper oxide nanoparticles (CuO-NP) are increasingly used in consumer-related products, which may result in increased oral ingestion. Digestion of particles can change their physicochemical properties and toxicity. Therefore, our aim was to simulate the gastrointestinal tract using a static in vitro digestion model. Toxic properties of digested and undigested CuO-NP were compared using an epithelial mono-culture (Caco-2) and a mucus-secreting co-culture model (Caco-2/HT29-MTX). Effects on intestinal barrier integrity, permeability, cell viability and apoptosis were analyzed. CuO-NP concentrations of 1, 10 and 100 µg mL^{-1} were used. Particle characterization by dynamic light scattering and transmission electron microscopy showed similar mean particle sizes before and after digestion, resulting in comparable delivered particle doses in vitro. Only slight effects on barrier integrity and cell viability were detected for 100 µg mL^{-1} CuO-NP, while the ion control $CuCl_2$ always caused significantly higher adverse effects. The utilized cell models were not significantly different. In summary, undigested and digested CuO-NP show comparable effects on the mono-/co-cultures, which are weaker than those of copper ions. Only in the highest concentration, CuO-NP showed weak effects on barrier integrity and cell viability. Nevertheless, a slightly increased apoptosis rate indicates existing cellular stress, which gives reason for further investigations.

Effects of Zinc Oxide Nanoparticles on Model Systems of the Intestinal Barrier.

Mittag A, Owesny P, Hoera C, Kämpfe A, Glei M.
Toxics **2022**, 10, 49.

Zinc oxide nanoparticles (ZnO NP) are often used in the food sector, among others, because of their advantageous properties. As part of the human food chain, they are inevitably taken up orally. The debate on the toxicity of orally ingested ZnO NP continues due to incomplete data. Therefore, the aim of our study was to examine the effects of two differently sized ZnO NP (<50 nm and <100 nm primary particle size; 123-614 µmol/L) on two model systems of the intestinal barrier. Differentiated Caco-2 enterocytes were grown on Transwell inserts in monoculture and also in coculture with the mucus-producing goblet cell line HT29-MTX. Although no comprehensive mucus layer was detectable in the coculture, cellular zinc uptake was clearly lower after a 24-h treatment with ZnO NP than in monocultured cells. ZnO NP showed no influence on the permeability, metabolic activity, cytoskeleton and cell nuclei. The transepithelial electrical resistance was significantly increased in the coculture model after treatment with ≥307 µmol/L ZnO NP. Only small zinc amounts (0.07-0.65 µg/mL) reached the basolateral area. Our results reveal that the cells of an intact intestinal barrier interact with ZnO NP but do not suffer serious damage.

Olive Oil Extracts and Oleic Acid Attenuate the LPS-Induced Inflammatory Response in Murine RAW264.7 Macrophages but Induce the Release of Prostaglandin E2.

Müller AK, Albrecht F, Rohrer C, Koeberle A, Werz O, Schlörmann W, Glei M, Lorkowski S, Wallert M.
Nutrients. **2021**, 13, 4437, doi: 10.3390/nu13124437.

Olive oil contains high amounts of oleic acid (OA). Although OA has been described to inhibit inflammatory processes, the effects of olive oil on cellular mechanisms remain poorly understood. Therefore, we compared the effects of major fatty acids (FA) from olive oil with those of olive oil extracts (OOE) on inflammatory mediators and alterations in the cellular phospholipid composition in murine macrophages. Upon treatment with different OOE, FA compositions of lipopolysaccharide (LPS)-stimulated murine RAW264.7 macrophages were analyzed using gas chromatography. Olive oil extracts and OA significantly reduced the LPS-induced expression of inducible nitric oxide synthase (iNos), cyclooxygenase (Cox2), and interleukin-6 mRNA. In addition, a significant decrease in Cox2 and iNos protein expression was observed. The formation of nitric oxide was significantly reduced, while the formation of prostaglandin (PG) E2 from arachidonic acid significantly increased after treatment with OOE or OA. The latter was associated with a shift in the phospholipid FA composition from arachidonic acid to OA, resulting in an elevated availability of arachidonic acid. Together, OOE and OA mediate anti-inflammatory effects in vitro but increase the release of arachidonic acid and hereinafter PGE2, likely due to elongation of OA and competitive incorporation of fatty acids into membrane phospholipids.

Pharmacological Inhibition of Factor XIIa Attenuates Abdominal Aortic Aneurysm, Reduces Atherosclerosis, and Stabilizes Atherosclerotic Plaques.

Searle AK*, Chen YC*, Wallert M*, McFadyen JD, Maluenda AC, Noonan J, Kanellakis P, Zaldivia MTK, Huang A, Lioe H, Biondo M, Nolte MW, Rossato P, Bobik A, Panousis C, Wang X, Hosseini H, Peter K.
Thromb Haemost. 2022, 122, 196, doi: 10.1055/a-1663-8208.

Background: 3F7 is a monoclonal antibody targeting the enzymatic pocket of activated factor XII (FXIIa), thereby inhibiting its catalytic activity. Given the emerging role of FXIIa in promoting thromboinflammation, along with its apparent redundancy for hemostasis, the selective inhibition of FXIIa represents a novel and highly attractive approach targeting pathogenic processes that cause thromboinflammation-driven cardiovascular diseases.
Methods: The effects of FXIIa inhibition were investigated using three distinct mouse models of cardiovascular disease-angiotensin II-induced abdominal aortic aneurysm (AAA), an ApoE-/- model of atherosclerosis, and a tandem stenosis model of atherosclerotic plaque instability. 3F7 or its isotype control, BM4, was administered to mice (10 mg/kg) on alternate days for 4 to 8 weeks, depending on the experimental model. Mice were examined for the development and size of AAAs, or the burden and instability of atherosclerosis and associated markers of inflammation.
Results: Inhibition of FXIIa resulted in a reduced incidence of larger AAAs, with less acute aortic ruptures and an associated fibro-protective phenotype. FXIIa inhibition also decreased stable atherosclerotic plaque burden and achieved plaque stabilization associated with increased deposition of fibrous structures, a >2-fold thicker fibrous cap, increased cap-to-core ratio, and reduction in localized and systemic inflammatory markers.
Conclusion: Inhibition of FXIIa attenuates disease severity across three mouse models of thromboinflammation-driven cardiovascular diseases. Specifically, the FXIIa-inhibiting monoclonal antibody 3F7 reduces AAA severity, inhibits the development of atherosclerosis, and stabilizes vulnerable plaques. Ultimately, clinical trials in patients with cardiovascular diseases such as AAA and atherosclerosis are warranted to demonstrate the therapeutic potential of FXIIa inhibition.

Mechanistic insights into p53-regulated cytotoxicity of combined entinostat and irinotecan against colorectal cancer cells

Marx C,Sonnemann J, Beyer M, Maddocks ODK, Lilla S, Hauzenberger I, Piée-Staffa A,Siniuk K, Nunna S, Marx-Blümel L, Westermann M, Wagner T, Meyer FB, Thierbach R, Mullins CS, Kdimati S, Linnebacher M, Neri F, Heinzel T, Wang Z, Krämer OH.
Mol Oncol **2021** 15, 3404.

Late-stage colorectal cancer (CRC) is still a clinically challenging problem. The activity of the tumor suppressor p53 is regulated via post-translational modifications (PTMs). While the relevance of p53 C-terminal acetylation for transcriptional regulation is well defined, it is unknown whether this PTM controls mitochondrially mediated apoptosis directly. We used wild-type p53 or p53-negative human CRC cells, cells with acetylation-defective p53, transformation assays, CRC organoids, and xenograft mouse models to assess how p53 acetylation determines cellular stress responses. The topoisomerase-1 inhibitor irinotecan induces acetylation of several lysine residues within p53. Inhibition of histone deacetylases (HDACs) with the class I HDAC inhibitor entinostat synergistically triggers mitochondrial damage and apoptosis in irinotecan-treated p53-positive CRC cells. This specifically relies on the C-terminal acetylation of p53 by CREB-binding protein/p300 and the presence of C-terminally acetylated p53 in complex with the proapoptotic BCL2 antagonist/killer protein. This control of C-terminal acetylation by HDACs can mechanistically explain why combinations of irinotecan and entinostat represent clinically tractable agents for the therapy of p53-proficient CRC.

Butyrate and Metformin Affect Energy Metabolism Independently of the Metabolic Phenotype in the Tumor Therapy Model

Meyer FB, Marx C, Spangel SB, Thierbach R.
Biomolecules **2021** 11, 1831.

The BALB/c cell transformation assay (BALB-CTA) considers inter- and intra-tumor heterogeneities and affords the possibility of a direct comparison between untransformed and malignant cells. In the present study, we established monoclonal cell lines that originate from the BALB-CTA and mimic heterogeneous tumor cell populations, in order to investigate phenotype-specific effects of the anti-diabetic drug metformin and the short-chain fatty acid butyrate. Growth inhibitory effects were measured with a ViCell XR cell counter. The BALB/c tumor therapy model (BALB-TTM) was performed, and the extracellular glucose level was measured in the medium supernatant. Using a Seahorse Analyzer, the metabolic phenotypes of four selected clones were characterized, and effects on energy metabolism were investigated. Anti-carcinogenic effects and reduced glucose uptake after butyrate application were observed in the BALB-TTM. Metabolic characterization of the cell clones revealed three different phenotypes. Surprisingly, treatment with metformin or butyrate induced opposite metabolic shifts with similar patterns in all cell clones tested. In conclusion, the BALB-TTM is a relevant model for mechanistic cancer research, and the generation of monoclonal cell lines offers a novel possibility to investigate specific drug effects in a heterogeneous tumor cell population. The results indicate that induced alterations in energy metabolism seem to be independent of the original metabolic phenotype.

Nutrient intake and nutrition status in vegetarians and vegans in comparison to omnivores - the Nutritional Evaluation (NuEva) study. Dawczynski C*, Weidauer T,

Richert C, Schlattmann P, Dawczynski K, Kiehntopf M.
Frontiers in Nutrition **2022** (accepted in January 2022). https://doi: 10.3389/fnut.2022.819106

Introduction: In recent years, vegetarian and vegan diets became increasingly important as they are associated with beneficial health outcomes. The NuEva study compares the impact of flexitarian, vegetarian, or vegan diets with omnivorous nutritional habits on nutrient intake and risk factors for non-communicable diseases.
Methods: A dietary protocol was kept over five days and blood and 24h urine samples were collected to examine the impact of dietary habits (omnivores, n = 65 (Median / Interquartile range: 33 / 17 yrs.), flexitarians, n = 70 (30 / 17 yrs.), ovo-lacto vegetarians, n = 65 (28 / 14 yrs.), vegans, n = 58 (25 / 10 yrs.)) on nutrient intake, nutrient concentrations in plasma, serum or 24h urine, body composition, and blood lipids.
Results: The increased exclusion of animal-based foods in the diet (omnivores < flexitarians < vegetarians < vegans) is associated with a decreased intake of energy, saturated fat, cholesterol, disaccharides, and total sugar as well an increased intake of dietary fibres, beta carotene, vitamin E and K.
The combined index of the B12 status (4cB12 score) in vegetarians (0.02 / 0.75) was lower compared to omnivores (0.34 / 0.58; $p \leq 0.05$) and flexitarians (0.24 / 0.52; $p \leq 0.05$). In omnivores vitamin A, vitamin E, ferritin, and the urinary excretion of selenium, iodine, and zinc were higher than in vegans ($p \leq 0.05$). In contrast, vegans had the highest concentrations of biotin, folate, and vitamin C.
Flexitarians, vegetarians, and vegans had a lower body weight, BMI, and body fat percentage in comparison to omnivores ($p \leq 0.05$).
In omnivores the concentrations on total cholesterol, LDL cholesterol, LDL cholesterol/HDL cholesterol ratio, apolipoprotein B, and apolipoprotein B/ apolipoprotein A1 ratio were higher than in vegetarians and vegans ($p \leq 0.05$).
Conclusion: The NuEva study confirms the position of the Academy of Nutrition and Dietetics that adequately planned vegetarian diets are healthy, nutritionally adequate, and may

provide health benefits in the prevention and treatment of non-communicable diseases. Nevertheless, critical nutrients were identified for all groups studied. This highlights the need to develop individual nutritional concepts to ensure an adequate nutrient intake.

UVB-exposed wheat germ oil increases serum 25-hydroxyvitamin D 2 without improving overall vitamin D status: a randomized controlled trial.

Bailer AC, Philipp S, Staudt S, Weidauer T, Kiehntopf M, Lorkowski S, Stangl GI, Dawczynski C. Eur J Nutr **2022**. https://doi: 10.1007/s00394-022-02827-w

Purpose: This study investigated whether UVB-exposed wheat germ oil (WGO) is capable to improving the vitamin D status in healthy volunteers.
Methods: A randomized controlled human-intervention trial in parallel design was conducted in Jena (Germany) between February and April. Ultimately, 46 healthy males and females with low mean 25-hydroxyvitamin D (25(OH)D) levels (34.9 ± 10.6 nmol/L) were randomized into three groups receiving either no WGO oil (control, n = 14), 10 g non-exposed WGO per day (- UVB WGO, n = 16) or 10 g WGO, which was exposed for 10 min to ultraviolet B-light (UVB, intensity 500-630 µW/cm2) and provided 23.7 µg vitamin D (22.9 µg vitamin D2 and 0.89 µg vitamin D3) (+ UVB WGO, n = 16) for 6 weeks. Blood was obtained at baseline, after 3 and 6 weeks and analyzed for serum vitamin D-metabolite concentrations via LC-MS/MS.
Results: Participants who received the UVB-exposed WGO were characterized by an increase of circulating 25(OH)D2 after 3 and 6 weeks of intervention. However, the 25(OH)D3 concentrations decreased in the + UVB WGO group, while they increased in the control groups. Finally, the total 25(OH)D concentration (25(OH)D2 + 25(OH)D3) in the + UVB WGO group was lower than that of the non-WGO receiving control group after 6 weeks of treatment. In contrast, circulating vitamin D (vitamin D2 + vitamin D3) was higher in the + UVB WGO group than in the control group receiving no WGO.
Conclusion: UVB-exposed WGO containing 23.7 µg vitamin D can increase 25(OH)D2 levels but do no improve total serum levels of 25(OH)D of vitamin D-insufficient subjects.
Trial registration: ClinicalTrials.gov: NCT03499327 (registered, April 13, 2018).

Gender- and subgroup-specific sensitivity analysis of alcohol consumption and mortality in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study.

Moissl AP, Delgado GA, Krämer BK, Dawczynski C, Stojakovic T, März W, Kleber ME, Lorkowski S. Data in Brief **2022**. https://doi.org/10.1016/j.dib.2022.107873

This Data in Brief article contains further sensitivity analysis data related to the article "Alcohol consumption and mortality: the Ludwigshafen Risk and Cardiovascular Health (LURIC) study" [1]. Alcohol consumption data of participants in LURIC was collected using a questionnaire. This data was used to calculate the amount of alcohol consumption in g ethanol per day by using standard volumes and standard vol-% in different beverages in Germany. The data shown here provide results from the LURIC study stratified by gender. Furthermore, the LURIC study results were reproduced using other classifications, which were stratified in different literature data. In addition, our analysis provides data of alcohol consumption for smokers and non-smokers in the LURIC study cohort separately.

Einfluss von n-3- und n-6-Fettsäuren auf das kardiovaskuläre Risiko – aktueller Stand der Forschung und praktische Bezüge für die Ernährungstherapie.

Dawczynski C, Dawczynski K. Ernährungs Umschau **2021**; 11: M650 - M661.

Aktueller Stand der Forschung und praktische Bezüge für die Ernährungstherapie

Mehrfach ungesättigte Fettsäuren (polyunsaturated fatty acids; PUFA) zeichnen sich durch zwei oder mehr Kohlenstoff-Doppelbindungen aus. Je nach Position der ersten Doppelbindung vom Methylende werden n-6- oder n-3-Fettsäuren unterschieden, die sich in ihrer Wirkung auf den Stoffwechsel unterscheiden. Der Beitrag erläutert aktuelle wissenschaftliche Daten zu den Wirkungen von n-3- und n-6-PUFA auf Herz-Kreislauf-Erkrankungen und chronische Entzündungen.

Diagnostic performance of rapid antigen testing for SARS-CoV-2: The COVid-19 AntiGen (COVAG) study

Wertenauer C, Brenner Michael G, Dressel A, Pfeifer C, Hauser U, Wieland E, Mayer C, Mutschmann C, Roskos M, Wertenauer HJ, Moissl AP, Lorkowski S, März W
Front Med **2022**; 9:774550. DOI: 10.3389/fmed.2022.774550

Background: Rapid diagnostic testing for SARS-Cov-2 antigens is used to combat the ongoing pandemic. In this study we aimed to compare two RDTs, the SD Biosensor Q SARS-CoV-2 Rapid Antigen Test (Roche) and the Panbio COVID-19 Ag Rapid Test (Abbott), against rRT-PCR.
Methods: We included 2,215 all-comers at a diagnostic center between February 1 and March 31, 2021. rRT-PCR-positive samples were examined for SARS-CoV-2 variants.
Findings: Three hundred and thirty eight participants (15%) were rRT-PCR-positive for SARS-CoV-2. The sensitivities of Roche-RDT and Abbott-RDT were 60.4 and 56.8% ($P < 0.0001$) and specificities 99.7% and 99.8% ($P = 0.076$). Sensitivity inversely correlated with rRT-PCR-Ct values. The RDTs had higher sensitivities in individuals referred by treating physicians (79.5%, 78.7%) than in those referred by health departments (49.5%, 44.3%) or tested for other reasons (50%, 45.8%), in persons without any comorbidities (74.4%, 71%) compared to those with comorbidities (38.2%, 34.4%), in individuals with COVID-19 symptoms (75.2%, 74.3%) compared to those without (31.9%, 23.3%), and in the absence of SARS-CoV-2 variants (87.7%, 84%) compared to Alpha variant carriers (77.1%, 72.3%). If 10,000 symptomatic individuals are tested of which 500 are truly positive, the RDTs would generate 38 false-positive and 124 false-negative results. If 10,000 asymptomatic individuals are tested, including 50 true positives, 18 false-positives and 34 false-negatives would be generated.
Interpretation: The sensitivities of the two RDTs for asymptomatic SARS-CoV-2 carriers are unsatisfactory. Their widespread use may not be effective in the ongoing SARS-CoV-2 pandemic. The virus genotype influences the sensitivity of the two RDTs. RDTs should be evaluated for different SARS-CoV-2 variants.

Burden of non-communicable diseases among adolescents aged 10-24 years in the EU, 1990-2019: a systematic analysis of the Global Burden of Diseases Study 2019

Armocida B, Monasta L, Sawyer S, Bustreo F, Segafredo G, Castelpietra G, Ronfani L, Pasovic M, Hay S; GBD 2019 Europe NCDs in Adolescents Collaborators, Perel P, Beran D
Lancet Child Adolesc Health 2022; in press. DOI: 10.1016/S2352-4642(22)00073-6

Background: Disability and mortality burden of non-communicable diseases (NCDs) have risen worldwide; however, the NCD burden among adolescents remains poorly described in the EU.
Methods: Estimates were retrieved from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019. Causes of NCDs were analysed at three different levels of the GBD 2019 hierarchy, for which mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life-years (DALYs) were extracted. Estimates, with the 95% uncertainty intervals (UI), were retrieved for EU Member States from 1990 to 2019, three age subgroups (10-14 years, 15-19 years, and 20-24 years), and by sex. Spearman's correlation was conducted between DALY rates for NCDs and the Socio-demographic Index (SDI) of each EU Member State.

Findings: In 2019, NCDs accounted for 86·4% (95% uncertainty interval 83·5-88·8) of all YLDs and 38·8% (37·4-39·8) of total deaths in adolescents aged 10-24 years. For NCDs in this age group, neoplasms were the leading causes of both mortality (4·01 [95% uncertainty interval 3·62-4·25] per 100 000 population) and YLLs (281·78 [254·25-298·92] per 100 000 population), whereas mental disorders were the leading cause for YLDs (2039·36 [1432·56-2773·47] per 100 000 population) and DALYs (2040·59 [1433·96-2774·62] per 100 000 population) in all EU Member States, and in all studied age groups. In 2019, among adolescents aged 10-24 years, males had a higher mortality rate per 100 000 population due to NCDs than females (11·66 [11·04-12·28] vs 7·89 [7·53-8·23]), whereas females presented a higher DALY rate per 100 000 population due to NCDs (8003·25 [5812·78-10 701·59] vs 6083·91 [4576·63-7857·92]). From 1990 to 2019, mortality rate due to NCDs in adolescents aged 10-24 years substantially decreased (-40·41% [-43·00 to -37·61), and also the YLL rate considerably decreased (-40·56% [-43·16 to -37·74]), except for mental disorders (which increased by 32·18% [1·67 to 66·49]), whereas the YLD rate increased slightly (1·44% [0·09 to 2·79]). Positive correlations were observed between DALY rates and SDIs for substance use disorders (r_s=0·58, p=0·0012) and skin and subcutaneous diseases (r_s=0·45, p=0·017), whereas negative correlations were found between DALY rates and SDIs for cardiovascular diseases (r_s=-0·46, p=0·015), neoplasms (r_s=-0·57, p=0·0015), and sense organ diseases (r_s=-0·61, p=0·0005).
Interpretation: NCD-related mortality has substantially declined among adolescents in the EU between 1990 and 2019, but the rising trend of YLL attributed to mental disorders and their YLD burden are concerning. Differences by sex, age group, and across EU Member States highlight the importance of preventive interventions and scaling up adolescent-responsive health-care systems, which should prioritise specific needs by sex, age, and location.

Global, regional, and national burden of diseases and injuries for adults 70 years and older: systematic analysis for the Global Burden of Disease 2019 Study

GBD 2019 Ageing Collaborators.
BMJ **2022**; 376:e068208. DOI: 10.1136/bmj-2021-068208

Objectives: To use data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019) to estimate mortality and disability trends for the population aged ≥70 and evaluate patterns in causes of death, disability, and risk factors.
Design: Systematic analysis.
Setting: Participants were aged ≥70 from 204 countries and territories, 1990-2019.
Main outcomes measures: Years of life lost, years lived with disability, disability adjusted life years, life expectancy at age 70 (LE-70), healthy life expectancy at age 70 (HALE-70), proportion of years in ill health at age 70 (PYIH-70), risk factors, and data coverage index were estimated based on standardised GBD methods.
Results: Globally the population of older adults has increased since 1990 and all cause death rates have decreased for men and women. However, mortality rates due to falls increased between 1990 and 2019. The probability of death among people aged 70-90 decreased, mainly because of reductions in non-communicable diseases. Globally disability burden was largely driven by functional decline, vision and hearing loss, and symptoms of pain. LE-70 and HALE-70 showed continuous increases since 1990 globally, with certain regional disparities. Globally higher LE-70 resulted in higher HALE-70 and slightly increased PYIH-70. Sociodemographic and healthcare access and quality indices were positively correlated with HALE-70 and LE-70. For high exposure risk factors, data coverage was moderate, while limited data were available for various dietary, environmental or occupational, and metabolic risks.
Conclusions: Life expectancy at age 70 has continued to rise globally, mostly because of decreases in chronic diseases. Adults aged ≥70 living in high income countries and regions with better healthcare access and quality were found to experience the highest life expectancy and healthy life expectancy. Disability burden, however, remained constant, suggesting the need to enhance public health and intervention programmes to improve wellbeing among older adults.

Socio-economic deprivation and COVID-19 in Germany

Moissl AP, Lorkowski S, März W
Scand J Public Health **2022**; in press. DOI: 10.1177/14034948221080397

No abstract available.

Mitochondrial genome-wide analysis of nuclear DNA methylation quantitative trait loci

Laaksonen J, Mishra PP, Seppälä I, Raitoharju E, Marttila S, Mononen N, Lyytikäinen LP, Kleber ME, Delgado GE, Lepistö M, Almusa H, Ellonen P, Lorkowski S, März W, Hutri-Kähönen N, Raitakari O, Kähönen M, Salonen JT, Lehtimäki T
Hum Mol Genet **2021**; in press. DOI: 10.1093/hmg/ddab339

Mitochondria have a complex communication network with the surrounding cell and can alter nuclear DNA methylation (DNAm). Variation in the mitochondrial DNA (mtDNA) has also been linked to differential DNAm. Genome-wide association studies have identified numerous DNAm quantitative trait loci, but these studies have not examined the mitochondrial genome. Herein, we quantified nuclear DNAm from blood and conducted a mitochondrial genome-wide association study of DNAm, with an additional emphasis on sex- and prediabetes-specific heterogeneity. We used the Young Finns Study (n = 926) with sequenced mtDNA genotypes as a discovery sample and sought replication in the Ludwigshafen Risk and Cardiovascular Health study (n = 2317). We identified numerous significant associations in the discovery phase ($P < 10-9$), but they were not replicated when accounting for multiple testing. In total, 27 associations were nominally replicated with a $P < 0.05$. The replication analysis presented no evidence of sex- or prediabetes-specific heterogeneity. The 27 associations were included in a joint meta-analysis of the two cohorts, and 19 DNAm sites associated with mtDNA variants, while four other sites showed haplogroup associations. An expression quantitative trait methylation analysis was performed for the identified DNAm sites, pinpointing two statistically significant associations. This study provides evidence of a mitochondrial genetic control of nuclear DNAm with little evidence found for sex- and prediabetes-specific effects. The lack of a comparable mtDNA data set for replication is a limitation in our study and further studies are needed to validate our results.

Dietary protein intake and health-related outcomes: a methodological protocol for the evidence evaluation and the outline of an evidence to decision framework underlying the evidence-based guideline of the German Nutrition Society

Kroke A, Schmidt A, Amini AM, Kalotai N, Lehmann A, Haardt J, Bauer JM, Bischoff-Ferrari HA, Boeing H, Egert S, Ellinger S, Kühn T, Louis S, Lorkowski S, Nimptsch K, Remer T, Schulze MB, Siener R, Stangl GI, Volkert D, Zittermann A, Buyken AE, Watzl B, Schwingshackl L; German Nutrition Society
Eur J Nutr **2022**; in press. DOI: 10.1007/s00394-021-02789-5

Purpose: The present work aimed to delineate (i) a revised protocol according to recent methodological developments in evidence generation, to (ii) describe its interpretation, the assessment of the overall certainty of evidence and to (iii) outline an Evidence to Decision framework for deriving an evidence-based guideline on quantitative and qualitative aspects of dietary protein intake.
Methods: A methodological protocol to systematically investigate the association between dietary protein intake and several health outcomes and for deriving dietary protein intake recommendations for the primary prevention of various non-communicable diseases in the general adult population was developed.
Results: The developed methodological protocol relies on umbrella reviews including systematic reviews with or without meta-analyses. Systematic literature searches in three

databases will be performed for each health-related outcome. The methodological quality of all selected systematic reviews will be evaluated using a modified version of AMSTAR 2, and the outcome-specific certainty of evidence for systematic reviews with or without meta-analysis will be assessed with NutriGrade. The general outline of the Evidence to Decision framework foresees that recommendations in the derived guideline will be given based on the overall certainty of evidence as well as on additional criteria such as sustainability.
Conclusion: The methodological protocol permits a systematic evaluation of published systematic reviews on dietary protein intake and its association with selected health-related outcomes. An Evidence to Decision framework will be the basis for the overall conclusions and the resulting recommendations for dietary protein intake.

Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019

GBD 2019 Dementia Forecasting Collaborators
Lancet Public Health **2022**; 7(2):e105-e125. DOI: 10.1016/S2468-2667(21)00249-8

Background: Given the projected trends in population ageing and population growth, the number of people with dementia is expected to increase. In addition, strong evidence has emerged supporting the importance of potentially modifiable risk factors for dementia. Characterising the distribution and magnitude of anticipated growth is crucial for public health planning and resource prioritisation. This study aimed to improve on previous forecasts of dementia prevalence by producing country-level estimates and incorporating information on selected risk factors.
Methods: We forecasted the prevalence of dementia attributable to the three dementia risk factors included in the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019 (high body-mass index, high fasting plasma glucose, and smoking) from 2019 to 2050, using relative risks and forecasted risk factor prevalence to predict GBD risk-attributable prevalence in 2050 globally and by world region and country. Using linear regression models with education included as an additional predictor, we then forecasted the prevalence of dementia not attributable to GBD risks. To assess the relative contribution of future trends in GBD risk factors, education, population growth, and population ageing, we did a decomposition analysis.
Findings: We estimated that the number of people with dementia would increase from 57·4 (95% uncertainty interval 50·4-65·1) million cases globally in 2019 to 152·8 (130·8-175·9) million cases in 2050. Despite large increases in the projected number of people living with dementia, age-standardised both-sex prevalence remained stable between 2019 and 2050 (global percentage change of 0·1% [-7·5 to 10·8]). We estimated that there were more women with dementia than men with dementia globally in 2019 (female-to-male ratio of 1·69 [1·64-1·73]), and we expect this pattern to continue to 2050 (female-to-male ratio of 1·67 [1·52-1·85]). There was geographical heterogeneity in the projected increases across countries and regions, with the smallest percentage changes in the number of projected dementia cases in high-income Asia Pacific (53% [41-67]) and western Europe (74% [58-90]), and the largest in north Africa and the Middle East (367% [329-403]) and eastern sub-Saharan Africa (357% [323-395]). Projected increases in cases could largely be attributed to population growth and population ageing, although their relative importance varied by world region, with population growth contributing most to the increases in sub-Saharan Africa and population ageing contributing most to the increases in east Asia.
Interpretation: Growth in the number of individuals living with dementia underscores the need for public health planning efforts and policy to address the needs of this group. Country-level estimates can be used to inform national planning efforts and decisions. Multifaceted approaches, including scaling up interventions to address modifiable risk factors and investing in research on biological mechanisms, will be key in addressing the expected increases in the number of individuals affected by dementia.

Meta-analyses identify DNA methylation associated with kidney function and damage

Schlosser P, …Lorkowski S, …Teumer A
Nat Commun **2021**; 12(1):7174. DOI: 10.1038/s41467-021-27234-3

Chronic kidney disease is a major public health burden. Elevated urinary albumin-to-creatinine ratio is a measure of kidney damage, and used to diagnose and stage chronic kidney disease. To extend the knowledge on regulatory mechanisms related to kidney function and disease, we conducted a blood-based epigenome-wide association study for estimated glomerular filtration rate (n = 33,605) and urinary albumin-to-creatinine ratio (n = 15,068) and detected 69 and seven CpG sites where DNA methylation was associated with the respective trait. The majority of these findings showed directionally consistent associations with the respective clinical outcomes chronic kidney disease and moderately increased albuminuria. Associations of DNA methylation with kidney function, such as CpGs at JAZF1, PELI1 and CHD2 were validated in kidney tissue. Methylation at PHRF1, LDB2, CSRNP1 and IRF5 indicated causal effects on kidney function. Enrichment analyses revealed pathways related to hemostasis and blood cell migration for estimated glomerular filtration rate, and immune cell activation and response for urinary albumin-to-creatinineratio-associated CpGs.

Epigenome-wide association study of serum urate reveals insights into urate co-regulation and the SLC2A9 locus

Tin A, …Lorkowski S, … Köttgen A
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Elevated serum urate levels, a complex trait and major risk factor for incident gout, are correlated with cardiometabolic traits via incompletely understood mechanisms. DNA methylation in whole blood captures genetic and environmental influences and is assessed in transethnic meta-analysis of epigenome-wide association studies (EWAS) of serum urate (discovery, n = 12,474, replication, n = 5522). The 100 replicated, epigenome-wide significant ($p < 1.1E-7$) CpGs explain 11.6% of the serum urate variance. At SLC2A9, the serum urate locus with the largest effect in genome-wide association studies (GWAS), five CpGs are associated with SLC2A9 gene expression. Four CpGs at SLC2A9 have significant causal effects on serum urate levels and/or gout, and two of these partly mediate the effects of urate-associated GWAS variants. In other genes, including SLC7A11 and PHGDH, 17 urate-associated CpGs are associated with conditions defining metabolic syndrome, suggesting that these CpGs may represent a blood DNA methylation signature of cardiometabolic risk factors. This study demonstrates that EWAS can provide new insights into GWAS loci and the correlation of serum urate with other complex traits.

The α-tocopherol-derived long-chain metabolite α-13'-COOH mediates endotoxin tolerance and modulates the inflammatory response via MAPK and NFκB pathways

Schubert M, Kluge S, Brunner E, Pace S, Birringer M, Werz O, Lorkowski S
Free Radic Biol Med **2022**; 178:83-96. DOI: 10.1016/j.freeradbiomed.2021.11.032

Scope: The long-chain metabolites of (LCM) vitamin E are proposed as the active regulatory metabolites of vitamin E providing, with their anti-inflammatory properties, an explanatory approach for the inconsistent effects of vitamin E on inflammatory-driven diseases. We examined the modulation of cytokine expression and release from macrophages, a fundamental process in many diseases, to gain insights into the anti-inflammatory mechanisms of the α-tocopherol-derived LCM α-13'-COOH.
Methods and results: Suppressed gene expression of C-C motif chemokine ligand 2 (Ccl2), tumor necrosis factor (Tnf), and interleukin (Il) 6 in response to lipopolysaccharides by 24 h pre-treatment with α-13'-COOH in RAW264.7 macrophages was revealed using quantitative

reverse transcription PCR. Further, reduced secretion of IL1β and CCL2 was found in this setup using flow cytometry. In contrast, 1 h pre-treatment suppressed only CCL2. Consequent gene expression analysis within 24 h of α-13'-COOH treatment revealed the induction of mitogen-activated protein kinases (MAPK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) negative feedback regulators including the 'master regulators' dual-specificity phosphatase 1 (Dusp1/Mkp1) and tumor necrosis factor induced protein 3 (Tnfaip3/A20). Approaches with immunoblots and chemical antagonists suggest a feedback induction via activation of extracellular-signal regulated kinase (ERK), p38 MAPK and NFκB pathways.
Conclusions: CCL2 is suppressed in murine macrophages by α-13'-COOH and the indirect suppression of MAPK and NFκB pathways is likely a relevant process contributing to anti-inflammatory actions of α-13'-COOH. These results improve the understanding of the effects of α-13'-COOH and provide a basis for new research strategies in the context of inflammatory diseases.

Factor H-related protein 1 (FHR-1) is associated with atherosclerotic cardiovascular disease

Irmscher S, Zipfel SLH, Halder LD, Ivanov L, Gonzalez-Delgado A, Waldeyer C, Seiffert M, Brunner FJ, von der Heide M, Löschmann I, Wulf S, Czamara D, Papac-Milicevic N, Strauß O, Lorkowski S, Reichenspurner H, Holers MV, Banda NK, Zeller T, Binder EB, Binder CJ, Wiech T, Zipfel PF, Skerka C
Sci Rep **2021**; 11(1):22511. DOI: 10.1038/s41598-021-02011-w

Atherosclerotic cardiovascular disease (ACVD) is a lipid-driven inflammatory disease and one of the leading causes of death worldwide. Lipid deposits in the arterial wall lead to the formation of plaques that involve lipid oxidation, cellular necrosis, and complement activation, resulting in inflammation and thrombosis. The present study found that homozygous deletion of the CFHR1 gene, which encodes the plasma complement protein factor H-related protein 1 (FHR-1), was protective in two cohorts of patients with ACVD, suggesting that FHR-1 accelerates inflammation and exacerbates the disease. To test this hypothesis, FHR-1 was isolated from human plasma and was found to circulate on extracellular vesicles and to be deposited in atherosclerotic plaques. Surface-bound FHR-1 induced the expression of pro-inflammatory cytokines and tissue factor in both monocytes and neutrophils. Notably, plasma concentrations of FHR-1, but not of factor H, were significantly ($p < 0.001$) elevated in patients with ACVD, and correlated with the expression of the inflammation markers C-reactive protein, apolipoprotein serum amyloid protein A, and neopterin. FHR-1 expression also significantly correlated with plasma concentrations of low-density lipoprotein (LDL) ($p < 0.0001$) but not high-density lipoprotein (HDL). Taken together, these findings suggest that FHR-1 is associated with ACVD.

Global, regional, and national mortality among young people aged 10-24 years, 1950-2019: a systematic analysis for the Global Burden of Disease Study 2019

GBD 2019 Adolescent Mortality Collaborators
Lancet **2021**; 398(10311):1593-1618. DOI: 10.1016/S0140-6736(21)01546-4

Background: Documentation of patterns and long-term trends in mortality in young people, which reflect huge changes in demographic and social determinants of adolescent health, enables identification of global investment priorities for this age group. We aimed to analyse data on the number of deaths, years of life lost, and mortality rates by sex and age group in people aged 10-24 years in 204 countries and territories from 1950 to 2019 by use of estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019.
Methods: We report trends in estimated total numbers of deaths and mortality rate per 100 000 population in young people aged 10-24 years by age group (10-14 years, 15-19 years,

and 20-24 years) and sex in 204 countries and territories between 1950 and 2019 for all causes, and between 1980 and 2019 by cause of death. We analyse variation in outcomes by region, age group, and sex, and compare annual rate of change in mortality in young people aged 10-24 years with that in children aged 0-9 years from 1990 to 2019. We then analyse the association between mortality in people aged 10-24 years and socioeconomic development using the GBD Socio-demographic Index (SDI), a composite measure based on average national educational attainment in people older than 15 years, total fertility rate in people younger than 25 years, and income per capita. We assess the association between SDI and all-cause mortality in 2019, and analyse the ratio of observed to expected mortality by SDI using the most recent available data release (2017).
Findings: In 2019 there were 1·49 million deaths (95% uncertainty interval 1·39-1·59) worldwide in people aged 10-24 years, of which 61% occurred in males. 32·7% of all adolescent deaths were due to transport injuries, unintentional injuries, or interpersonal violence and conflict; 32·1% were due to communicable, nutritional, or maternal causes; 27·0% were due to non-communicable diseases; and 8·2% were due to self-harm. Since 1950, deaths in this age group decreased by 30·0% in females and 15·3% in males, and sex-based differences in mortality rate have widened in most regions of the world. Geographical variation has also increased, particularly in people aged 10-14 years. Since 1980, communicable and maternal causes of death have decreased sharply as a proportion of total deaths in most GBD super-regions, but remain some of the most common causes in sub-Saharan Africa and south Asia, where more than half of all adolescent deaths occur. Annual percentage decrease in all-cause mortality rate since 1990 in adolescents aged 15-19 years was 1·3% in males and 1·6% in females, almost half that of males aged 1-4 years (2·4%), and around a third less than in females aged 1-4 years (2·5%). The proportion of global deaths in people aged 0-24 years that occurred in people aged 10-24 years more than doubled between 1950 and 2019, from 9·5% to 21·6%.
Interpretation: Variation in adolescent mortality between countries and by sex is widening, driven by poor progress in reducing deaths in males and older adolescents. Improving global adolescent mortality will require action to address the specific vulnerabilities of this age group, which are being overlooked. Furthermore, indirect effects of the COVID-19 pandemic are likely to jeopardise efforts to improve health outcomes including mortality in young people aged 10-24 years. There is an urgent need to respond to the changing global burden of adolescent mortality, address inequities where they occur, and improve the availability and quality of primary mortality data in this age group.

Einfluss der Ernährung auf Herz-Kreislauf-Erkrankungen

Lorkowski S
VFED aktuell Herz im Fokus – Ernährung, Prävention und Therapie **2022**:10-24.

No abstract available.

Herzgesund Essen: Ernährung in der Primärprävention und Therapie von Herz-Kreislauf-Erkrankungen

Schumacher S, Dawczynski C, Lorkowski S
VFED aktuell Herz im Fokus – Ernährung, Prävention und Therapie **2022**:43-53.

No abstract available.

Health promoting effects of secondary plant products

Böhm V.
Acta Hortic. **2021**, 1329, 123-132.

Carotenoids and polyphenols are two groups of secondary plant products often focused by the media due to their possible health promoting effects. Interestingly, these compounds are synthesized by plants to protect themselves against UV stress, insects, microorganisms, etc. In recent decades, epidemiological studies demonstrated health-related effects of these plant ingredients for humans. Various biological activities were discovered in in-vitro experiments, in cell experiments and in animal studies. The gold standard are human intervention studies, which are not yet done for all secondary plant products. Carotenoids are lipophilic antioxidants with several other properties while polyphenols are widespread hydrophilic antioxidants. Lutein is a yellow coloured carotenoid, comprised in green leafy vegetables. There, lutein protects the chlorophyll against UV radiation. The same preventive effects have been demonstrated for human skin. Another part of the human body needing UV protection is the macula lutea, the yellow spot in the eye. Destruction of the macula results in age-related macular degeneration (AMD). In many human intervention studies, lutein intake out of supplements and food items improved the macular pigment optical density (MPOD) and thus was an AMD prevention. Two human intervention trials are presented showing MPOD improvement after regular intake of lutein and zeaxanthin out of a supplement or a food. Apples are consumed very often as fruits or as products thereof. They are a good source of various polyphenols, improving the antioxidant status. In addition, birch pollen-related apple allergy was influenced by apple polyphenols. Apple allergenicity decreased especially after enzymatic browning. In vitro experiments showed inverse correlations between contents of polyphenols as well as polyphenol oxidase activity and in vitro allergic reactions, partly explaining why old apple cultivars are better tolerated by apple allergy sufferers. These are only two examples of health-promoting effects of secondary plant products.

Phytochemical analysis, antioxidant, antibacterial, and cytotoxic activities of leaves and roots of Rubus hyrcanus Juz.
Yousefbeyk, F., Ghasemi, S., Evazalipour, M., Dabirian, S., Schubert, C., Hekmatnia, S., Habibi, Y, Koohi, D. E., Böhm, V.:
Eur. Food Res. Technol. **2022**, 248, 141-152.

Rubus hyrcanus Juz. (Rosaceae), known as Caspian blackberry, is wildly distributed around the Caspian Sea. This study focused on antioxidant, cytotoxic, and antibacterial activities of total extracts and different fractions from the roots and leaves of this species. The total phenolics and flavonoid contents were also evaluated. Finally, the phenolic profiles of selected fractions were determined using HPLC–DAD and LC–MS/MS. The results indicated that the total phenolics content (TPC) of root total extract (RTE) was 3.5 times that of leaves (340.4 and 102.7 mg GAE/g, respectively). The TPC of three root fractions ranged from 226.6 to 392.9 mg GAE/g, while in leaves fractions, it ranged between 68.3 and 101.8 mg GAE/g. The total extract of leaves had higher contents of total flavonoids than roots (70.5 and 8.9 mg QE/g, respectively). The methanol fractions of both parts had the highest amounts of flavonoids. The root methanol fraction (RMF) had the best antioxidant effect in both DPPH radical scavenging assay (IC50: 9.16 µg ml−1) and total antioxidant capacity test (1010.5 mg αTE/g). The RMF and RTE had potent antibacterial activities against Bacillus subtilis and Staphylococcus aureus (MIC 1.5 mg ml−1). In the MTT assay, ethyl acetate fractions of roots and leaves exhibited the best cytotoxicity (IC50 247 and 227 µg ml−1, respectively) and the highest selectivity indexes (4.73 and 5.31, respectively). Phytochemical analysis revealed the presence of gallic acid, p-coumaric acid, and chlorogenic acid in leaves ethyl acetate fraction, chlorogenic acid in leaves methanol fraction, and gallic acid in the root ethyl acetate fraction.

A comprehensive review on carotenoids in foods and feeds: status quo, applications, patents and needs
Meléndez-Martínez, … Böhm, V.,… O'Brien, N.:
Crit. Rev. Food Sci. Nutr. **2022**, 62, 1999-2049.

Carotenoids are isoprenoids widely distributed in foods that have been always part of the diet of humans. Unlike the other so-called food bioactives, some carotenoids can be converted into retinoids exhibiting vitamin A activity, which is essential for humans. Furthermore, they are much more versatile as they are relevant in foods not only as sources of vitamin A, but also as natural pigments, antioxidants, and health-promoting compounds. Lately, they are also attracting interest in the context of nutricosmetics, as they have been shown to provide cosmetic benefits when ingested in appropriate amounts. In this work, resulting from the collaborative work of participants of the COST Action European network to advance carotenoid research and applications in agrofood and health (EUROCAROTEN, www.eurocaroten.eu, https://www.cost.eu/actions/CA15136/#tabsjName:overview) research on carotenoids in foods and feeds is thoroughly reviewed covering aspects such as analysis, carotenoid food sources, carotenoid databases, effect of processing and storage conditions, new trends in carotenoid extraction, daily intakes, use as human, and feed additives are addressed. Furthermore, classical and recent patents regarding the obtaining and formulation of carotenoids for several purposes are pinpointed and briefly discussed. Lastly, emerging research lines as well as research needs are highlighted.

Egg yolk colour in organic production as affected by feeding – Consequences for farmers and consumers
Sünder, A., Wilkens, M., Böhm, V., Liebert, F.:
Food Chem. **2022**, 382, 131854.

In organic table egg production, saponified extracts of carotenoids are not allowed to intensify egg yolk colour. Therefore, we investigated the suitability of organically produced marigold flower meal (Tagetes erectus, TE) and spinach (Spinacia oleracea, SO) as carotenoid sources (mixture of 25% TE and 75% SO) to reach values of 9–10 'Roche Yolk Colour Fan' units (RYCF units). Feeding a completely unsupplemented control diet resulted in a yolk colour of 4.7 RYCF units, a total supply of 11.1 g/kg, 14.6 g/kg and 17.5 g/kg of TE and SO as stand-alone carotenoid sources induced a significant increase to 8.0, 8.2 and 8.9 RYCF units. Under 'winter-feeding conditions', i.e. minimal carotenoid supply in the diet, 17.5 g/kg TE and SO resulted in 9.3 ± 0.7 RYCF units. It can be concluded that supplementing TE and SO is suitable to improve the yolk colour in organically produced table eggs.

FOXO transcription factors in antioxidant defense.
Krafczyk N, Klotz LO.
IUBMB Life. **2022** Jan;74(1):53-61. (doi: 10.1002/iub.2542.)

Forkhead box, class O (FOXO) family proteins are widely expressed and highly conserved transcriptional regulators that modulate cellular fuel metabolism, stress resistance and cell death. FOXO target genes include genes encoding antioxidant proteins, thus likely contributing to the key role FOXOs play in the cellular response to oxidative stress and supporting the cellular strategies of antioxidant defense, that is, prevention (of the formation of reactive oxygen species), interception (of reactive species prior to their reaction with cellular components), repair (of damaged biomolecules), and adaptation (i.e., the stimulation of signaling pathways allowing for the expression of protective proteins). FOXOs themselves are regulated by redox processes at several levels, including expression of FOXO genes and enzymatic as well as nonenzymatic posttranslational modifications of FOXO proteins. The latter include modifications of FOXO cysteine residues. Here, an overview is provided on (i) the contribution of FOXO target genes to cellular antioxidative strategies, and (ii) on the impact of thiol homeostasis and thiol modification on FOXO activity.

SEMO-1, a novel methanethiol oxidase in Caenorhabditis elegans, is a pro-aging factor conferring selective stress resistance.

Philipp TM, Gong W, Köhnlein K, Ohse VA, Müller FI, Priebs J, Steinbrenner H, Klotz LO.
Biofactors. **2022** Mar 22. (doi: 10.1002/biof.1836.)

Methanethiol is a toxic gas produced through bacterial degradation of sulfur-containing amino acids. Applying a novel enzymatic assay, we here identified a methanethiol oxidase (MTO) that catalyzes the degradation of methanethiol in the nematode Caenorhabditis elegans (C. elegans). The corresponding protein, Y37A1B.5, previously characterized as a C. elegans ortholog of human selenium-binding protein 1 (SELENBP1), was renamed SEMO-1 (SELENBP1 ortholog with methanethiol oxidase activity). Worms rendered deficient in SEMO-1 not only showed decreased hydrogen sulfide production from methanethiol catabolism but they were also more resistant to oxidative stress and had an elevated life span. In contrast, resistance to selenite was significantly lowered in SEMO-1-deficient worms. Naturally occurring mutations of human SELENBP1 were introduced to recombinant SEMO-1 through site-directed mutagenesis and resulted in loss of its MTO activity, indicating a similar enzymatic mechanism for SELENBP1 and SEMO-1. In summary, SEMO-1 confers resistance to toxic selenite and the ability to metabolize toxic methanethiol. These beneficial effects might be a trade-off for its negative impact on C. elegans life span.

The role of selenium in type-2 diabetes mellitus and its metabolic comorbidities.

Steinbrenner H, Duntas LH, Rayman MP.
Redox Biol. **2022** Apr;50:102236. (doi: 10.1016/j.redox.2022.102236.)

This review addresses the role of the essential trace element, selenium, in type-2 diabetes mellitus (T2DM) and its metabolic co-morbidities, i.e., metabolic syndrome, obesity and non-alcoholic fatty liver disease. We refer to the dietary requirements of selenium and the key physiological roles of selenoproteins. We explore the dysregulated fuel metabolism in T2DM and its co-morbidities, emphasizing the relevance of inflammation and oxidative stress. We describe the epidemiology of observational and experimental studies of selenium in diabetes and related conditions, explaining that the interaction between selenium status and glucose control is not limited to hyperglycemia but extends to hypoglycemia. We propose that the association between high plasma/serum selenium and T2DM/fasting plasma glucose observed in many cross-sectional studies may rely on the upregulation of hepatic selenoprotein-P biosynthesis in conditions of hyperglycemia and insulin resistance. While animal studies have revealed potential molecular mechanisms underlying adverse effects of severe selenium/selenoprotein excess and deficiency in the pathogenesis of insulin resistance and β-cell dysfunction, their translational significance is rather limited. Importantly, dietary selenium supplementation does not appear to be a major causal factor for the development of T2DM in humans though we cannot currently exclude a small contribution of selenium on top of other risk factors, in particular if it is ingested at high (supranutritional) doses. Elevated selenium biomarkers that are often measured in T2DM patients are more likely to be a consequence, rather than a cause, of diabetes.