Neues aus der Wissenschaft
Wissenschaftliche Publikationen aus dem Institut für Ernährungswissenschaften der Friedrich-Schiller-Universität Jena veröffentlicht von Mai 2023 bis Oktober 2023

Simultaneous quantitation of oxidized and reduced glutathione via LC-MS/MS to study the redox state and drug-mediated modulation in cells, worms and animal tissue.
Thiel A, Weishaupt AK, Nicolai MM, Lossow K, Kipp AP, Schwerdtle T, Bornhorst J.
J Chromatogr B Analyt Technol Biomed Life Sci. (2023);1225:123742.

Alterations in reduced and oxidized glutathione (GSH/GSSG) levels represent an important marker for oxidative stress and potential disease progression in toxicological research. Since GSH can be oxidized rapidly, using a stable and reliable method for sample preparation and GSH/GSSG quantification is essential to obtain reproducible data. Here we describe an optimised sample processing combined with a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, validated for different biological matrices (lysates from HepG2 cells, C. elegans, and mouse liver tissue). To avoid autoxidation of GSH, samples were treated with the thiol-masking agent N-ethylmaleimide (NEM) and sulfosalicylic acid (SSA) in a single step. With an analysis time of 5 min, the developed LC-MS/MS method offers simultaneous determination of GSH and GSSG at high sample throughput with high sensitivity. This is especially interesting with respect of screening for oxidative and protective properties of substances in in vitro and in vivo models, e.g. C. elegans. In addition to method validation parameters (linearity, limit of detection (LOD), limit of quantification (LOQ), recovery, interday, intraday), we verified the method by using menadione and L-buthionine-(S,R)-sulfoximine (BSO) as well established modulators of cellular GSH and GSSG concentrations. Thereby menadione proved to be a reliable positive control also in C. elegans.

Excessive copper impairs intrahepatocyte trafficking and secretion of selenoprotein P.
Schwarz M, Meyer CE, Löser A, Lossow K, Hackler J, Ott C, Jäger S, Mohr I, Eklund EA, Patel AAH, Gul N, Alvarez S, Altinonder I, Wiel C, Maares M, Haase H, Härtlova A, Grune T, Schulze MB, Schwerdtle T, Merle U, Zischka H, Sayin VI, Schomburg L, Kipp AP.
Nat Commun. (2023);14(1):3479.

Selenium homeostasis depends on hepatic biosynthesis of selenoprotein P (SELENOP) and SELENOP-mediated transport from the liver to e.g. the brain. In addition, the liver maintains copper homeostasis. Selenium and copper metabolism are inversely regulated, as increasing copper and decreasing selenium levels are observed in blood during aging and inflammation. Here we show that copper treatment increased intracellular selenium and SELENOP in hepatocytes and decreased extracellular SELENOP levels. Hepatic accumulation of copper is a characteristic of Wilson's disease. Accordingly, SELENOP levels were low in serum of Wilson's disease patients and Wilson's rats. Mechanistically, drugs targeting protein transport in the Golgi complex mimicked some of the effects observed, indicating a disrupting effect of excessive copper on intracellular SELENOP transport resulting in its accumulation in the late Golgi. Our data suggest that hepatic copper levels determine SELENOP release from the liver and may affect selenium transport to peripheral organs such as the brain.

Selenium, Zinc, and Copper Status of Vegetarians and Vegans in Comparison to Omnivores in the Nutritional Evaluation (NuEva) Study.
Klein L, Dawczynski C, Schwarz M, Maares M, Kipp K, Haase H, Kipp AP.
Nutrients. (2023);15(16):3538.

Plant-based diets usually contain more nutrient-dense foods such as vegetables, legumes, whole grains, and fruits than a standard Western diet. Yet, the amount and especially the bioavailability of several nutrients, such as trace elements, is supposed to be lower in comparison to diets with consumption of animal-derived foods. Based on this, the Nutritional Evaluation (NuEva) study (172 participants) was initiated to compare the trace element status of omnivores, flexitarians, vegetarians, and vegans. Serum selenium, zinc, and copper concentrations and biomarkers were evaluated at baseline and during a 12-month intervention with energy- and nutrient-optimized menu plans. The implementation of optimized menu plans did not substantially influence the status of trace elements. At baseline, serum selenium biomarkers were lower in vegetarians and vegans compared to omnivores and flexitarians. The zinc intake of vegetarians and vegans was significantly lower compared to omnivores, whereas the Phytate Diet Score was increased. Accordingly, total serum zinc concentrations were reduced in vegans which was, however, only significant in women and was further supported by the analysis of free zinc. Regarding copper status, no differences were observed for total serum copper. Overall, we identified selenium and zinc as critical nutrients especially when maintaining a vegan diet.

Temporal dynamics of muscle mitochondrial uncoupling-induced integrated stress response and ferroptosis defense.
Igual Gil C, Löser A, Lossow K, Schwarz M, Weber D, Grune T, Kipp AP, Klaus S, Ost M.
Front Endocrinol (Lausanne). 2023 Oct 23;14:1277866. doi: 10.3389/fendo.2023.1277866. eCollection 2023.

Mitochondria play multifaceted roles in cellular function, and impairments across domains of mitochondrial biology are known to promote cellular integrated stress response (ISR) pathways as well as systemic metabolic adaptations. However, the temporal dynamics of specific mitochondrial ISR related to physiological variations in tissue-specific energy demands remains unknown. Here, we conducted a comprehensive 24-hour muscle and plasma profiling of male and female mice with ectopic mitochondrial respiratory uncoupling in skeletal muscle (mUcp1-transgenic, TG). TG mice are characterized by increased muscle ISR, elevated oxidative stress defense, and increased secretion of FGF21 and GDF15 as ISR-induced myokines. We observed a temporal signature of both cell-autonomous and systemic ISR in the context of endocrine myokine signaling and cellular redox balance, but not of ferroptotic signature which was also increased in TG muscle. We show a progressive increase of muscle ISR on transcriptional level during the active phase (night time), with a subsequent peak in circulating FGF21 and GDF15 in the early resting phase. Moreover, we found highest levels of muscle oxidative defense (GPX and NQO1 activity) between the late active to early resting phase, which could aim to counteract excessive iron-dependent lipid peroxidation and ferroptosis in muscle of TG mice. These findings highlight the temporal dynamics of cell-autonomous and endocrine ISR signaling under skeletal muscle mitochondrial uncoupling, emphasizing the importance of considering such dissociation in translational strategies and sample collection for diagnostic biomarker analysis.

Requirement of transcription-coupled nucleotide excision repair for the removal of a specific type of oxidatively induced DNA damage
Sarmini L, Meabed M, Emmanouil E, Atsaves G, Robeska E, Karwowski BT, Campalans A, Gimisis T, Khobta A.
Nucleic Acids Research 51(10) (2023) 4982-4994

Accumulation of DNA damage resulting from reactive oxygen species was proposed to cause neurological and degenerative disease in patients, deficient in nucleotide excision repair (NER) or its transcription-coupled subpathway (TC-NER). Here, we assessed the requirement of TC-NER for the repair of specific types of oxidatively generated DNA modifications. We incorporated synthetic 5',8-cyclo-2'-deoxypurine nucleotides (cyclo-dA, cyclo-dG) and thymine glycol (Tg) into an EGFP reporter gene to measure transcription-blocking potentials of these modifications in human cells. Using null mutants, we further identified the relevant DNA repair components by a host cell reactivation approach. The results indicated that NTHL1-initiated base excision repair is by far the most efficient pathway for Tg. Moreover, Tg was efficiently bypassed during transcription, which effectively rules out TC-NER as an alternative repair mechanism. In a sharp contrast, both cyclopurine lesions robustly blocked transcription and were repaired by NER, wherein the specific TC-NER components CSB/ERCC6 and CSA/ERCC8 were as essential as XPA. Instead, repair of classical NER substrates, cyclobutane pyrimidine dimer and N-(deoxyguanosin-8-yl)-2-acetylaminofluorene, occurred even when TC-NER was disrupted. The strict requirement of TC-NER highlights cyclo-dA and cyclo-dG as candidate damage types, accountable for cytotoxic and degenerative responses in individuals affected by genetic defects in this pathway.

Evaluation of Influencing Factors on Metabolism of Land-Based n-3 Poly Unsaturated Fatty Acids—The KoALA Study.
Drobner T, Braun TS, Kiehntopf M, Schlattmann P, Lorkowski S, Dawczynski C.
Nutrients 15(20) (2023) 4461. https://doi.org/10.3390/nu15204461

This study aimed to investigate the impact of influencing factors (sex, eicosapentaenoic acid (EPA) status at baseline, linoleic acid (LA) intake, milk fat intake) on the conversion of α-linolenic acid (ALA) obtained from linseed oil into its long-chain metabolites. In addition, the effect of ALA on cardiovascular risk markers was investigated. This study used a parallel design approach by randomly assigning the 134 subjects to one of four diets (high in LA (HLA); low in LA (LLA); high in milk fat (MF); control (Western diet)) each enriched with linseed oil (10 en%, 22-27 mL ≙ 13-16 g ALA). Blood samples were taken at baseline and after 4, 8, and 12 weeks of dietary intervention. The study was fully completed by 105 subjects (57.4 ± 12.1 years; 65.7% female). Results showed that ALA (296-465%), C-20:4n3 (54-140%), and EPA (37-73%) concentrations in erythrocytes increased in all groups ($p < 0.01$). In contrast, docosahexaenoic acid (19-35%, $p < 0.01$) and n-3 index (10-21%, $p < 0.05$) dropped in the HLA, LLA, and control groups. An increase in C-22:5n3 was only observed in the MF (36%) and control groups (11%) ($p < 0.05$). In addition, an increase in LA (7-27%) was found in the HLA, LLA, and control groups, whereas C-20:3n6 (16-22%), arachidonic acid (10-16%), C-22:4n6 (12-30%), and C-22:5n6 (32-47%) decreased ($p < 0.01$). The conversion into EPA was higher in men than in women (69 vs. 39%, $p = 0.043$) and in subjects with low EPA status compared to participants with high EPA status (79 vs. 29%, $p < 0.001$). A high LA status attenuates the conversion rate. In line with the literature, no clear effects on blood lipids and parameters of glucose metabolism were found in relation to ALA supplementation.

Variability in Macro- and Micronutrients of 15 Rarely Researched Microalgae.
Sandgruber F, Gielsdorf A, Schenz B, Müller SM, Schwerdtle T, Lorkowski S, Griehl C, Dawczynski C.
Marine Drugs 21(6) (2023) 355. https://doi.org/10.3390/md21060355

Microalgae have enormous potential for human nutrition, yet the European Commission has authorized the consumption of only eleven species. Strains of fifteen rarely researched microalgae from two kingdoms were screened regarding their nutritional profile and value for human health in two cultivation phases. Contents of protein, fiber, lipids, fatty acids, minerals, trace elements and heavy metals were determined. In the growth phase, microalgae accumulated more arginine, histidine, ornithine, pure and crude protein, Mg, Mn, Fe and Zn and less Ni, Mo and I2 compared to the stationary phase. Higher contents of total fat, C14:0, C14:1n5, C16:1n7, C20:4n6, C20:5n3 and also As were observed in microalgae from the chromista kingdom in comparison to microalgae from the plantae kingdom ($p < 0.05$). Conversely, the latter had higher contents of C20:0, C20:1n9 and C18:3n3 as well as Ca and Pb ($p < 0.05$). More precisely, Chrysotila carterae appeared to have great potential for human nutrition because of its high nutrient contents such as fibers, carotenoids, C20:6n3, Mg, Ca, Mn, Fe, Se, Zn, Ni, Mo and I2. In summary, microalgae may contribute to a large variety of nutrients, yet the contents differ between kingdoms, cultivation phases and also species.

Human nutritional relevance and suggested nutritional guidelines for vitamin A5/X and provitamin A5/X.
Bohn, T., Hellman-Regen, J., de Lera, A. R., Böhm, V., Rühl, R.
Nutrition & Metabolism 20 (2023) 34

In the last century, vitamin A was identified that included the nutritional relevant vitamin A1 / provitamin A1, as well as the vitamin A2 pathway concept. Globally, nutritional guidelines have focused on vitamin A1 with simplified recommendations and calculations based solely on vitamin A. The vitamin A / provitamin A terminology described vitamin A with respect to acting as a precursor of 11-cis-retinal, the chromophore of the visual pigment, as well as retinoic acid(s), being ligand(s) of the nuclear hormone receptors retinoic acid receptors (RARs) α, β and γ. All-trans retinoic acid was conclusively shown to be the endogenous RAR ligand, while the concept of its isomer 9-cis-retinoic acid, being “the” endogenous ligand of the retinoid-X receptors (RXRs), remained inconclusive. Recently, 9-cis-13,14-dihydroretinoic acid was conclusively reported as an endogenous RXR ligand, and a direct nutritional precursor was postulated in 2018 and further confirmed by Rühl, Krezel and de Lera in 2021. This was further termed vitamin A5/X / provitamin A5/X. In this review, a new vitamin A5/X / provitamin A5/X concept is conceptualized in parallel to the vitamin A(1) / provitamin A(1) concept for daily dietary intake and towards dietary guidelines, with a focus on the existing national and international regulations for the physiological and nutritional relevance of vitamin A5/X. The aim of this review is to summarize available evidence and to emphasize gaps of knowledge regarding vitamin A5/X, based on new and older studies and proposed future directions as well as to stimulate and propose adapted nutritional regulations.

Effect of hydrostatic pressure and temperature on extractability and bioaccessibility of lipophilic micronutrients in kale.
Schmidt, M., Hopfhauer, S., Schneider, F., Ivanovic, J., Schwarzenbolz, U., Böhm, V.
ACS Food Science & Technology 3 (2023) 1122-1135

High-pressure processing (HPP) represents a sustainable and gentle preservation technique. Since the effects of processing parameters are still poorly reported for lipophilic, bioactive ingredients (e.g., vitamin E and carotenoids), the present study covers a comprehensive set of HP applications using laboratory-, pilot-, and industrial-scale plants to evaluate nutritional aspects such as compound extractabilities, bioaccessibilities, and antioxidant capacities. Low-pressure regimes increased extractabilities of vitamin E in kale at 10 MPa (+105%) and at 50 MPa (+102%). Multicycle processing had no significant contribution to the extractability of target compounds. Thermally processed samples (40−80 °C) at 600 MPa retained major chlorophyll content in contrast to depletion after heat sterilization (121 °C). HPP improved the bioaccessibilities of vitamin E, lutein, and β-carotene even at 600 MPa (80 °C). Industrial-scale samples at high-pressure, low-temperature showed a more fresh-like texture elicited by a reduced need for sample comminution and optimal conditions for increased extractabilities of target compounds.

Selenium-binding protein 1 (SELENBP1) is a copper-dependent thiol oxidase.
Philipp TM, Gernoth L, Will A, Schwarz M, Ohse VA, Kipp AP, Steinbrenner H, Klotz LO.
Redox Biol. 2023; 65:102807. doi: 10.1016/j.redox.2023.102807.

Selenium-binding protein 1 (SELENBP1) was reported to act as a methanethiol oxidase (MTO) in humans, catalyzing the conversion of methanethiol to hydrogen peroxide, hydrogen sulfide and formaldehyde. Here, we identify copper ions as essential to this novel MTO activity. Site-directed mutagenesis of putative copper-binding sites in human SELENBP1 produced as recombinant protein in E. coli resulted in loss of its enzymatic function. On the other hand, the eponymous binding of selenium (as selenite) was no requirement for MTO activity and only moderately increased SELENBP1-catalyzed oxidation of methanethiol. Furthermore, SEMO-1, the SELENBP1 ortholog recently identified in the nematode C. elegans, also requires copper ions, and MTO activity was enhanced or abrogated, respectively, if worms were grown in the presence of cupric chloride or of a Cu chelator. In addition to methanethiol, we identified novel substrates of SELENBP1 from the group of volatile sulfur compounds, ranging from ethanethiol to 1-pentanethiol as well as 2-propene-1-thiol. Gut microbiome-derived methanethiol as well as food-derived volatile sulfur compounds (VSCs) account for malodors that may contribute to extraoral halitosis in humans, if not metabolized properly. As SELENBP1 is particularly abundant in tissues exposed to VSCs, such as colon, liver, and lung, it appears to contribute to copper-dependent VSC degradation.

Nutrigenomics and redox regulation: Concepts relating to the Special Issue on nutrigenomics.
Klotz LO, Carlberg C.
Redox Biol. 2023; 68:102920. doi: 10.1016/j.redox.2023.102920.

During our whole lifespan, from conception to death, the epigenomes of all tissues and cell types of our body integrate signals from the environment. This includes signals derived from our diet and the uptake of macro- and micronutrients. In most cases, this leads only to transient changes, but some effects of this epigenome programming process are persistent and can even be transferred to the next generation. Both epigenetic programming and redox processes are affected by the individual choice of diet and other lifestyle decisions like physical activity. The nutrient-gene communication pathways have adapted during human evolution and are essential for maintaining health. However, when they are maladaptive, such as in long-term obesity, they significantly contribute to diseases like type 2 diabetes and cancer. The field of nutrigenomics investigates nutrition-related signal transduction pathways and their effect on gene expression involving interactions both with the genome and the epigenomes. Several of these diet-(epi)genome interactions and the involved signal transduction cascades are redox-regulated. Examples include the effects of the NAD+/NADH ratio, vitamin C levels and secondary metabolites of dietary molecules from plants on the acetylation and methylation state of the epigenome as well as on gene expression through redox-sensitive pathways via the transcription factors NFE2L2 and FOXO. In this review, we summarize and extend on these topics as well as those discussed in the articles of this Special Issue and take them into the context of redox biology.

Methanethiol: A Scent Mark of Dysregulated Sulfur Metabolism in Cancer.
Philipp TM, Scheller AS, Krafczyk N, Klotz LO, Steinbrenner H.
Antioxidants (Basel). 2023; 12:1780. doi: 10.3390/antiox12091780.

In order to cope with increased demands for energy and metabolites as well as to enhance stress resilience, tumor cells develop various metabolic adaptations, representing a hallmark of cancer. In this regard, the dysregulation of sulfur metabolism that may result in elevated levels of volatile sulfur compounds (VSCs) in body fluids, breath, and/or excretions of cancer patients has recently gained attention. Besides hydrogen sulfide (H2S), methanethiol is the predominant cancer-associated VSC and has been proposed as a promising biomarker for non-invasive cancer diagnosis. Gut bacteria are the major exogenous source of exposure to this foul-smelling toxic gas, with methanethiol-producing strains such as Fusobacterium nucleatum highly abundant in the gut microbiome of colorectal carcinoma (CRC) patients. Physiologically, methanethiol becomes rapidly degraded through the methanethiol oxidase (MTO) activity of selenium-binding protein 1 (SELENBP1). However, SELENBP1, which is considered a tumor suppressor, is often downregulated in tumor tissues, and this has been epidemiologically linked to poor clinical outcomes. In addition to impaired removal, an increase in methanethiol levels may derive from non-enzymatic reactions, such as a Maillard reaction between glucose and methionine, two metabolites enriched in cancer cells. High methionine concentrations in cancer cells may also result in enzymatic methanethiol production in mitochondria. Moreover, enzymatic endogenous methanethiol production may occur through methyltransferase-like protein 7B (METTL7B), which is present at elevated levels in some cancers, including CRC and hepatocellular carcinoma (HCC). In conclusion, methanethiol contributes to the scent of cancer as part of the cancer-associated signature combination of volatile organic compounds (VOCs) that are increasingly being exploited for non-invasive early cancer diagnosis.

Biologie des Alterns
Klotz LO, Simm A.
In: Alternsforschung – Handbuch für Wissenschaft und Studium (K. Hank, M. Wagner, S. Zank, eds.), 2. Auflage, Nomos Verlagsgesellschaft, Baden-Baden, Germany, pp. 85-111, 2023.

Nach Besprechung grundlegender Begrifflichkeiten zu biologischen Aspekten des Alterns geht das vorliegende Kapitel auf Mechanismen ein, die zur biologischen Alterung beitragen. Einer Vielzahl unterschiedlicher und vermutlich parallel ablaufender biologischer Mechanismen steht dabei als Gemeinsamkeit das Resultat der Alterung von Zellen, Geweben oder Organismen gegenüber: die Akkumulation geschädigter Biomoleküle, der Verlust der Reparatur- und Anpassungsfähigkeit, die Änderung von Signalprozessen. Das Kapitel liefert Beispiele für Mechanismen, die über evolutionsbiologische, deterministische oder stochastische Erklärungsansätze verstanden werden können, um eine Synthese über Erklärung der Modulation zellulärer Signalprozesse zu versuchen. Abschließend wird auf die Frage eingegangen, ob Biomarker des Alter(n)s existieren, und welche Maßnahmen biologische Alternsprozesse verlangsamen können.

Protein intake and body weight, fat mass and waist circumference: an umbrella review of systematic reviews for the evidence-based guideline on protein intake of the German Nutrition Society.
Ellinger S, Amini AM, Haardt J, Lehmann A, Schmidt A, Bischoff-Ferrari HA, Buyken AE, Kroke A, Kühn T, Louis S, Lorkowski S, Nimptsch K, Schulze MB, Schwingshackl L, Siener R, Stangl GI, Volkert D, Zittermann A, Watzl B, Egert S; German Nutrition Society.
European Journal of Nutrition 2023; im Druck.

Purpose: This umbrella review aimed to assess whether dietary protein intake with regard to quantitative (higher vs. lower dietary protein intake) and qualitative considerations (total, plant-based or animal-based protein intake) affects body weight (BW), fat mass (FM) and waist circumference (WC).
Methods: A systematic literature search was conducted in PubMed, Embase and Cochrane Database of Systematic Reviews for systematic reviews (SRs) with and without meta-analyses of prospective studies published between 04 October 2007 and 04 January 2022. Methodological quality and outcome-specific certainty of evidence of the retrieved SRs were assessed by using AMSTAR 2 and NutriGrade, respectively, in order to rate the overall certainty of evidence using predefined criteria.
Results: Thirty-three SRs were included in this umbrella review; 29 were based on randomised controlled trials, a few included cohort studies. In studies without energy restriction, a high-protein diet did not modulate BW, FM and WC in adults in general (all "possible" evidence); for older adults, overall certainty of evidence was "insufficient" for all parameters. Under hypoenergetic diets, a high-protein diet mostly decreased BW and FM, but evidence was "insufficient" due to low methodological quality. Evidence regarding an influence of the protein type on BW, FM and WC was "insufficient".
Conclusion: "Possible" evidence exists that the amount of protein does not affect BW, FM and WC in adults under isoenergetic conditions. Its impact on the reduction in BW and FM under hypoenergetic conditions remains unclear; evidence for an influence of protein type on BW, FM and WC is "insufficient".

Global burden of peripheral artery disease and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019.
GBD 2019 Peripheral Artery Disease Collaborators.
Lancet Global Health 2023; 11(10):e1553-e1565.

Background: Peripheral artery disease is a growing public health problem. We aimed to estimate the global disease burden of peripheral artery disease, its risk factors, and temporospatial trends to inform policy and public measures.
Methods: Data on peripheral artery disease were modelled using the Global Burden of Disease, Injuries, and Risk Factors Study (GBD) 2019 database. Prevalence, disability-adjusted life years (DALYs), and mortality estimates of peripheral artery disease were extracted from GBD 2019. Total DALYs and age-standardised DALY rate of peripheral artery disease attributed to modifiable risk factors were also assessed.
Findings: In 2019, the number of people aged 40 years and older with peripheral artery disease was 113 million (95% uncertainty interval [UI] 99·2-128·4), with a global prevalence of 1·52% (95% UI 1·33-1·72), of which 42·6% was in countries with low to middle Socio-demographic Index (SDI). The global prevalence of peripheral artery disease was higher in older people, (14·91% [12·41-17·87] in those aged 80-84 years), and was generally higher in females than in males. Globally, the total number of DALYs attributable to modifiable risk factors in 2019 accounted for 69·4% (64·2-74·3) of total peripheral artery disease DALYs. The prevalence of peripheral artery disease was highest in countries with high SDI and lowest in countries with low SDI, whereas DALY and mortality rates showed U-shaped curves, with the highest burden in the high and low SDI quintiles.
Interpretation: The total number of people with peripheral artery disease has increased globally from 1990 to 2019. Despite the lower prevalence of peripheral artery disease in males and low-income countries, these groups showed similar DALY rates to females and higher-income countries, highlighting disproportionate burden in these groups. Modifiable risk factors were responsible for around 70% of the global peripheral artery disease burden. Public measures could mitigate the burden of peripheral artery disease by modifying risk factors.

Establishment and characterization of mild atopic dermatitis in the DNCB-induced mouse model.
Riedl R, Kühn A, Rietz D, Hebecker B, Glowalla KG, Peltner LK, Jordan PM, Werz O, Lorkowski S, Wiegand C, Wallert M.
International Journal of Molecular Sciences 2023; 24(15):12325.

In dermatological research, 2,4-dinitrochlorbenzene (DNCB)-induced atopic dermatitis (AD) is a standard model as it displays many disease-associated characteristics of human AD. However, the reproducibility of the model is challenging due to the lack of information regarding the methodology and the description of the phenotype and endotype of the mimicked disease. In this study, a DNCB-induced mouse model was established with a detailed procedure description and classification of the AD human-like skin type. The disease was induced with 1% DNCB in the sensitization phase and repeated applications of 0.3% and 0.5% DNCB in the challenging phase which led to a mild phenotype of AD eczema. Pathophysiological changes of the dorsal skin were measured: thickening of the epidermis and dermis, altered skin barrier proteins, increased TH1 and TH2 cytokine expression, a shift in polyunsaturated fatty acids, increased pro-resolving and inflammatory mediator formation, and dysregulated inflammation-associated gene expression. A link to type I allergy reactions was evaluated by increased mast cell infiltration into the skin accompanied by elevated IgE and histamine levels in plasma. As expected for mild AD, no systemic inflammation was observed. In conclusion, this experimental setup demonstrates many features of a mild human-like extrinsic AD in murine skin.

Protein intake and type 2 diabetes mellitus: an umbrella review of systematic reviews for the evidence-based guideline for protein intake of the German Nutrition Society.
Schulze MB, Haardt J, Amini AM, Kalotai N, Lehmann A, Schmidt A, Buyken AE, Egert S, Ellinger S, Kroke A, Kühn T, Louis S, Nimptsch K, Schwingshackl L, Siener R, Zittermann A, Watzl B, Lorkowski S; German Nutrition Society.
European Journal of Nutrition 2023; im Druck.

Purpose: Protein-rich foods show heterogeneous associations with the risk of type 2 diabetes (T2D) and it remains unclear whether habitual protein intake is related to T2D risk. We carried out an umbrella review of systematic reviews (SR) of randomised trials and/or cohort studies on protein intake in relation to risks of T2D.
Methods: Following a pre-specified protocol (PROSPERO: CRD42018082395), we retrieved SRs on protein intake and T2D risk published between July 1st 2009 and May 22nd 2022, 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: Eight SRs were identified of which six contained meta-analyses. The majority of SRs on total protein intake had moderate or high methodological quality and moderate outcome-specific certainty of evidence according to NutriGrade, however, the latter was low for the majority of SRs on animal and plant protein. Six of the eight SRs reported risk increases with both total and animal protein. According to one SR, total protein intake in studies was ~ 21 energy percentage (%E) in the highest intake category and 15%E in the lowest intake category. Relative Risks comparing high versus low intake in most recent SRs ranged from 1.09 (two SRs, 95% CIs 1.02-1.15 and 1.06-1.13) to 1.11 (1.05-1.16) for total protein (between 8 and 12 cohort studies included) and from 1.13 (1.08-1.19) to 1.19 (two SRs, 1.11-1.28 and 1.11-1.28) (8-9 cohort studies) for animal protein. However, SRs on RCTs examining major glycaemic traits (HbA_{1c}, fasting glucose, fasting insulin) do not support a clear biological link with T2D risk. For plant protein, some recent SRs pointed towards risk decreases and non-linear associations, however, the majority did not support an association with T2D risk.
Conclusion: Higher total protein intake was possibly associated with higher T2D risk, while there is insufficient evidence for a risk increase with higher intakes of animal protein and a risk decrease with plant protein intake. Given that most SRs on plant protein did not indicate an association, there is possibly a lack of an effect.

α-Tocopherol-13'-carboxychromanol induces cell cycle arrest and cell death by inhibiting the SREBP1-SCD1 axis and causing imbalance in lipid desaturation.
Liao S, Gollowitzer A, Börmel L, Maier C, Gottschalk L, Werz O, Wallert M, Koeberle A, Lorkowski S.
International Journal of Molecular Sciences 2023; 24(11):9229.

α-Tocopherol-13'-carboxychromanol (α-T-13'-COOH) is an endogenously formed bioactive α-tocopherol metabolite that limits inflammation and has been proposed to exert lipid metabolism-regulatory, pro-apoptotic, and anti-tumoral properties at micromolar concentrations. The mechanisms underlying these cell stress-associated responses are, however, poorly understood. Here, we show that the induction of G_0/G_1 cell cycle arrest and apoptosis in macrophages triggered by α-T-13'-COOH is associated with the suppressed proteolytic activation of the lipid anabolic transcription factor sterol regulatory element-binding protein (SREBP)1 and with decreased cellular levels of stearoyl-CoA desaturase (SCD)1. In turn, the fatty acid composition of neutral lipids and phospholipids shifts from monounsaturated to saturated fatty acids, and the concentration of the stress-preventive, pro-survival lipokine 1,2-dioleoyl-*sn*-glycero-3-phospho-(1'-myo-inositol) [PI(18:1/18:1)] decreases. The selective inhibition of SCD1 mimics the pro-apoptotic and anti-proliferative activity of α-T-13'-COOH, and the provision of the SCD1 product oleic acid (C18:1) prevents α-T-13'-COOH-induced apoptosis. We conclude that micromolar concentrations of α-T-13'-COOH trigger cell death and likely also cell cycle arrest by suppressing the SREBP1-SCD1 axis and depleting cells of monounsaturated fatty acids and PI(18:1/18:1).

The global fatty liver disease Sustainable Development Goal country score for 195 countries and territories.

Lazarus JV, Han H, Mark HE, Alqahtani SA, Schattenberg JM, Soriano JB, White TM, Zelber-Sagi S, Dirac MA; GBD Fatty Liver Disease Sustainable Development Goal Collaborators.

Hepatology 2023; 78(3):911-928.

Background and aims: Fatty liver disease is highly prevalent, resulting in overarching wellbeing and economic costs. Addressing it requires comprehensive and coordinated multisectoral action. We developed a fatty liver disease Sustainable Development Goal (SDG) country score to provide insights into country-level preparedness to address fatty liver disease through a whole-of-society lens.

Approach and results: We developed 2 fatty liver disease-SDG score sets. The first included 6 indicators (child wasting, child overweight, noncommunicable disease mortality, a universal health coverage service coverage index, health worker density, and education attainment), covering 195 countries and territories between 1990 and 2017. The second included the aforementioned indicators plus an urban green space indicator, covering 60 countries and territories for which 2017 data were available. To develop the fatty liver disease-SDG score, indicators were categorized as "positive" or "negative" and scaled from 0 to 100. Higher scores indicate better preparedness levels. Fatty liver disease-SDG scores varied between countries and territories (n = 195), from 14.6 (95% uncertainty interval: 8.9 to 19.4) in Niger to 93.5 (91.6 to 95.3) in Japan; 18 countries and territories scored > 85. Regionally, the high-income super-region had the highest score at 88.8 (87.3 to 90.1) in 2017, whereas south Asia had the lowest score at 44.1 (42.4 to 45.8). Between 1990 and 2017, the fatty liver disease-SDG score increased in all super-regions, with the greatest increase in south Asia, but decreased in 8 countries and territories.

Conclusions: The fatty liver disease-SDG score provides a strategic advocacy tool at the national and global levels for the liver health field and noncommunicable disease advocates, highlighting the multisectoral collaborations needed to address fatty liver disease, and noncommunicable diseases overall.

High genetic risk for depression as an independent risk factor for mortality in patients referred for coronary angiography.

Krämer RM, Moissl AP, Lorkowski S, Krämer BK, Lehtimäki T, Mishra BH, Mishra PP, Leipe J, März W, Kleber ME, Müller-Myhsok B, Delgado GE.

Frontiers in Cardiovascular Medicine 2023; 10:1125151.

Background: Different observations have suggested that patients with depression have a higher risk for a number of comorbidities and mortality. The underlying causes have not been fully understood yet.

Aims: The aim of our study was to investigate the association of a genetic depression risk score (GDRS) with mortality [all-cause and cardiovascular (CV)] and markers of depression (including intake of antidepressants and a history of depression) in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study involving 3,316 patients who had been referred for coronary angiography.

Methods and results: The GDRS was calculated in 3,061 LURIC participants according to a previously published method and was found to be associated with all-cause (p = 0.016) and CV mortality (p = 0.0023). In Cox regression models adjusted for age, sex, body mass index, LDL-cholesterol, HDL-cholesterol, triglycerides, hypertension, smoking, and diabetes mellitus, the GDRS remained significantly associated with all-cause [1.18 (1.04-1.34, p = 0.013)] and CV [1.31 (1.11-1.55, p = 0.001)] mortality. The GDRS was not associated with the intake of antidepressants or a history of depression. However, this cohort of CV patients had not specifically been assessed for depression, leading to marked underreporting. We were unable to identify any specific biomarkers correlated with the GDRS in LURIC participants.

Conclusion: A genetic predisposition for depression estimated by a GDRS was independently associated with all-cause and CV mortality in our cohort of patients who had been referred for coronary angiography. No biomarker correlating with the GDRS could be identified.

A conceptual framework for adaptive personalized nutrition advice systems (APNASs).
Renner B, Buyken AE, Gedrich K, Lorkowski S, Watzl B, Linseisen J, Daniel H; working group “Personalized Nutrition” of the German Nutrition Society.
Advances in Nutrition 2023; 14(5):983-994.

Nearly all approaches to personalized nutrition (PN) use information such as the gene variants of individuals to deliver advice that is more beneficial than a generic "1-size-fits-all" recommendation. Despite great enthusiasm and the increased availability of commercial services, thus far, scientific studies have only revealed small to negligible effects on the efficacy and effectiveness of personalized dietary recommendations, even when using genetic or other individual information. In addition, from a public health perspective, scholars are critical of PN because it primarily targets socially privileged groups rather than the general population, thereby potentially widening health inequality. Therefore, in this perspective, we propose to extend current PN approaches by creating adaptive personalized nutrition advice systems (APNASs) that are tailored to the type and timing of personalized advice for individual needs, capacities, and receptivity in real-life food environments. These systems encompass a broadening of current PN goals (i.e., what should be achieved) to incorporate "individual goal preferences" beyond currently advocated biomedical targets (e.g., making sustainable food choices). Moreover, they cover the "personalization processes of behavior change" by providing in situ, "just-in-time" information in real-life environments (how and when to change), which accounts for individual capacities and constraints (e.g., economic resources). Finally, they are concerned with a "participatory dialog between individuals and experts" (e.g., actual or virtual dieticians, nutritionists, and advisors) when setting goals and deriving measures of adaption. Within this framework, emerging digital nutrition ecosystems enable continuous, real-time monitoring, advice, and support in food environments from exposure to consumption. We present this vision of a novel PN framework along with scenarios and arguments that describe its potential to efficiently address individual and population needs and target groups that would benefit most from its implementation.

Protein intake and bone health: an umbrella review of systematic reviews for the evidence-based guideline of the German Nutrition Society.
Zittermann A, Schmidt A, Haardt J, Kalotai N, Lehmann A, Egert S, Ellinger S, Kroke A, Lorkowski S, Louis S, Schulze MB, Schwingshackl L, Siener R, Stangl GI, Volkert D, Watzl B, Bischoff-Ferrari HA; German Nutrition Society.
Osteoporosis International 2023; 34(8):1335-1353.

This umbrella review aimed at assessing whether a protein intake exceeding the current recommendation for younger (0.8 g/kg body weight [BW]/day) and older (1.0 g/kg BW/day) adults affects bone mineral density and fracture risk. Moreover, the effect of animal or plant protein was evaluated. A systematic literature search was conducted in PubMed, Embase, and Cochrane Database of Systematic Reviews for systematic reviews (SRs) with or without meta-analysis of prospective studies published between 11/2008 and 08/2021. Methodological quality, outcome-specific certainty of evidence, and overall certainty of evidence of the retrieved SRs were assessed using established tools and predefined criteria. Eleven SRs of randomized controlled trials (RCTs) and/or cohort studies were included. In SRs of cohort studies and RCTs, protein intake/kg BW/day ranged between 0.21-0.95 g (low intake) and > 1.24 g (high intake), respectively, and between 0.67-1.1 g (control groups) and 1.01-1.69 g (intervention groups), respectively. The vast majority of outcome-specific certainty of evidence was rated "low" or "very low." The overall certainty of evidence for an association (cohort studies) or effect (RCTs) of total, animal or plant protein intake on each of the investigated outcomes was rated "insufficient," with the exception of possible evidence for a reduced hip fracture risk by high vs. low protein intake. Since protein intakes in low/control and high/intervention groups were very heterogeneous and with low certainty of evidence, it remains unclear whether a dose above the current recommendation or type of protein intake (animal or plant protein) affects bone health overall. However, there is possible evidence for reduced hip fracture risk with high versus low protein intake.

Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021.

GBD 2021 Diabetes Collaborators.

Lancet 2023; 402(10397):203-234.

Background: Diabetes is one of the leading causes of death and disability worldwide, and affects people regardless of country, age group, or sex. Using the most recent evidentiary and analytical framework from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), we produced location-specific, age-specific, and sex-specific estimates of diabetes prevalence and burden from 1990 to 2021, the proportion of type 1 and type 2 diabetes in 2021, the proportion of the type 2 diabetes burden attributable to selected risk factors, and projections of diabetes prevalence through 2050.

Methods: Estimates of diabetes prevalence and burden were computed in 204 countries and territories, across 25 age groups, for males and females separately and combined; these estimates comprised lost years of healthy life, measured in disability-adjusted life-years (DALYs; defined as the sum of years of life lost [YLLs] and years lived with disability [YLDs]). We used the Cause of Death Ensemble model (CODEm) approach to estimate deaths due to diabetes, incorporating 25 666 location-years of data from vital registration and verbal autopsy reports in separate total (including both type 1 and type 2 diabetes) and type-specific models. Other forms of diabetes, including gestational and monogenic diabetes, were not explicitly modelled. Total and type 1 diabetes prevalence was estimated by use of a Bayesian meta-regression modelling tool, DisMod-MR 2.1, to analyse 1527 location-years of data from the scientific literature, survey microdata, and insurance claims; type 2 diabetes estimates were computed by subtracting type 1 diabetes from total estimates. Mortality and prevalence estimates, along with standard life expectancy and disability weights, were used to calculate YLLs, YLDs, and DALYs. When appropriate, we extrapolated estimates to a hypothetical population with a standardised age structure to allow comparison in populations with different age structures. We used the comparative risk assessment framework to estimate the risk-attributable type 2 diabetes burden for 16 risk factors falling under risk categories including environmental and occupational factors, tobacco use, high alcohol use, high body-mass index (BMI), dietary factors, and low physical activity. Using a regression framework, we forecast type 1 and type 2 diabetes prevalence through 2050 with Socio-demographic Index (SDI) and high BMI as predictors, respectively.

Findings: In 2021, there were 529 million (95% uncertainty interval [UI] 500-564) people living with diabetes worldwide, and the global age-standardised total diabetes prevalence was 6·1% (5·8-6·5). At the super-region level, the highest age-standardised rates were observed in north Africa and the Middle East (9·3% [8·7-9·9]) and, at the regional level, in Oceania (12·3% [11·5-13·0]). Nationally, Qatar had the world's highest age-specific prevalence of diabetes, at 76·1% (73·1-79·5) in individuals aged 75-79 years. Total diabetes prevalence-especially among older adults-primarily reflects type 2 diabetes, which in 2021 accounted for 96·0% (95·1-96·8) of diabetes cases and 95·4% (94·9-95·9) of diabetes DALYs worldwide. In 2021, 52·2% (25·5-71·8) of global type 2 diabetes DALYs were attributable to high BMI. The contribution of high BMI to type 2 diabetes DALYs rose by 24·3% (18·5-30·4) worldwide between 1990 and 2021. By 2050, more than 1·31 billion (1·22-1·39) people are projected to have diabetes, with expected age-standardised total diabetes prevalence rates greater than 10% in two super-regions: 16·8% (16·1-17·6) in north Africa and the Middle East and 11·3% (10·8-11·9) in Latin America and Caribbean. By 2050, 89 (43·6%) of 204 countries and territories will have an age-standardised rate greater than 10%.

Interpretation: Diabetes remains a substantial public health issue. Type 2 diabetes, which makes up the bulk of diabetes cases, is largely preventable and, in some cases, potentially reversible if identified and managed early in the disease course. However, all evidence indicates that diabetes prevalence is increasing worldwide, primarily due to a rise in obesity caused by multiple factors. Preventing and controlling type 2 diabetes remains an ongoing challenge. It is essential to better understand disparities in risk factor profiles and diabetes burden across populations, to inform strategies to successfully control diabetes risk factors within the context of multiple and complex drivers.

Protein intake and risk of urolithiasis and kidney diseases: an umbrella review of systematic reviews for the evidence-based guideline of the German Nutrition Society.
Remer T, Kalotai N, Amini AM, Lehmann A, Schmidt A, Bischoff-Ferrari HA, Egert S, Ellinger S, Kroke A, Kühn T, Lorkowski S, Nimptsch K, Schwingshackl L, Zittermann A, Watzl B, Siener R; German Nutrition Society.
European Journal of Nutrition 2023; 62(5):1957-1975.

Purpose: Changes in dietary protein intake metabolically affect kidney functions. However, knowledge on potential adverse consequences of long-term higher protein intake (HPI) for kidney health is lacking. To summarise and evaluate the available evidence for a relation between HPI and kidney diseases, an umbrella review of systematic reviews (SR) was conducted.
Methods: PubMed, Embase and Cochrane Database of SRs published until 12/2022 were searched for the respective SRs with and without meta-analyses (MA) of randomised controlled trials or cohort studies. For assessments of methodological quality and of outcome-specific certainty of evidence, a modified version of AMSTAR 2 and the NutriGrade scoring tool were used, respectively. The overall certainty of evidence was assessed according to predefined criteria.
Results: Six SRs with MA and three SRs without MA on various kidney-related outcomes were identified. Outcomes were chronic kidney disease, kidney stones and kidney function-related parameters: albuminuria, glomerular filtration rate, serum urea, urinary pH and urinary calcium excretion. Overall certainty of evidence was graded as 'possible' for stone risk not to be associated with HPI and albuminuria not to be elevated through HPI (above recommendations (> 0.8 g/kg body weight/day)) and graded as 'probable' or 'possible' for most other kidney function-related parameters to be physiologically increased with HPI.
Conclusion: Changes of the assessed outcomes may have reflected mostly physiological (regulatory), but not pathometabolic responses to higher protein loads. For none of the outcomes, evidence was found that HPI does specifically trigger kidney stones or diseases. However, for potential recommendations long-term data, also over decades, are required.

Impact of regular intake of microalgae on nutrient supply and cardiovascular risk factors: results from the NovAL intervention study.
Sandgruber F, Höger AL, Kunze J, Schenz B, Griehl C, Kiehntopf M, Kipp K, Kühn J, Stangl GI, Lorkowski S, Dawczynski C.
Nutrients 2023; 15(7):1645.

A 14-day randomized controlled study with a parallel design was conducted with 80 healthy participants. Intervention groups I (IG1) and II (IG2) received a defined background diet and consumed a smoothie enriched with either 15 g of *Chlorella* dry weight (d.w.) or 15 g of *Microchloropsis* d.w. daily. Control group II (CG2) received a defined background diet without the smoothie. Control group I (CG1) received neither. Blood samples and 24-h urine were collected at the beginning and the end of the study. Serum concentrations of 25-hydroxyvitamin D_3, vitamin D_3, selenium, iron, ferritin, transferrin saturation, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol and the LDL-cholesterol/HDL cholesterol ratio decreased in IG1 ($p < 0.05$), while 25-hydroxyvitamin D_2 increased ($p < 0.05$). In IG2, vitamin D_3, 25-hydroxyvitamins D_2 and D_3 decreased ($p < 0.05$), while concentrations of fatty acids $C20:5_{n3}$ and $C22:5_{n3}$ increased. Serum and urine uric acid increased in IG1 and IG2 ($p < 0.05$). *Microchloropsis* is a valuable source of n3 fatty acids, as is *Chlorella* of vitamin D_2. Regular consumption of *Chlorella* may affect the iron and selenium status negatively but may impact blood lipids positively. An elevated uric acid concentration in blood and urine following the regular consumption of microalgae poses potential risks for human health.

DNA methylation analysis is used to identify novel genetic loci associated with circulating fibrinogen levels in blood.

Hahn J, Bressler J, Domingo-Relloso A, Chen MH, McCartney DL, Teumer A, van Dongen J, Kleber ME, Aïssi D, Swenson BR, Yao J, Zhao W, Huang J, Xia Y, Brown MR, Costeira R, de Geus EJC, Delgado GE, Dobson DA, Elliott P, Grabe HJ, Guo X, Harris SE, Huffman JE, Kardia SLR, Liu Y, Lorkowski S, Marioni RE, Nauck M, Ratliff SM, Sabater-Lleal M, Spector TD, Suchon P, Taylor KD, Thibord F, Trégouët DA, Wiggins KL, Willemsen G, Bell JT, Boomsma DI, Cole SA, Cox SR, Dehghan A, Greinacher A, Haack K, März W, Morange PE, Rotter JI, Sotoodehnia N, Tellez-Plaza M, Navas-Acien A, Smith JA, Johnson AD, Fornage M, Smith NL, Wolberg AS, Morrison AC, de Vries PS.
Journal of Thrombosis and Haemostasis 2023; 21(5):1135-1147.

Background: Fibrinogen plays an essential role in blood coagulation and inflammation. Circulating fibrinogen levels may be determined based on interindividual differences in DNA methylation at cytosine-phosphate-guanine (CpG) sites and vice versa.
Objectives: To perform an EWAS to examine an association between blood DNA methylation levels and circulating fibrinogen levels to better understand its biological and pathophysiological actions.
Methods: We performed an epigenome-wide association study of circulating fibrinogen levels in 18 037 White, Black, American Indian, and Hispanic participants, representing 14 studies from the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium. Circulating leukocyte DNA methylation was measured using the Illumina 450K array in 12 904 participants and using the EPIC array in 5133 participants. In each study, an epigenome-wide association study of fibrinogen was performed using linear mixed models adjusted for potential confounders. Study-specific results were combined using array-specific meta-analysis, followed by cross-replication of epigenome-wide significant associations. We compared models with and without CRP adjustment to examine the role of inflammation.
Results: We identified 208 and 87 significant CpG sites associated with fibrinogen levels from the 450K ($p < 1.03 \times 10^{-7}$) and EPIC arrays ($p < 5.78 \times 10^{-8}$), respectively. There were 78 associations from the 450K array that replicated in the EPIC array and 26 vice versa. After accounting for overlapping sites, there were 83 replicated CpG sites located in 61 loci, of which only 4 have been previously reported for fibrinogen. The examples of genes located near these CpG sites were SOCS3 and AIM2, which are involved in inflammatory pathways. The associations of all 83 replicated CpG sites were attenuated after CRP adjustment, although many remained significant.
Conclusion: We identified 83 CpG sites associated with circulating fibrinogen levels. These associations are partially driven by inflammatory pathways shared by both fibrinogen and CRP.