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Commentary

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The exposome and nutritional pharmacology and toxicology: a new application for metabolomics

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Abstract

The exposome refers to all of the internal and external life-long exposures that an individual experiences. These exposures, either acute or chronic, are associated with changes in metabolism that will positively or negatively influence the health and well-being of individuals. Nutrients and other dietary compounds modulate similar biochemical processes and have the potential in some cases to counteract the negative effects of exposures or enhance their beneficial effects. We present herein the concept of Nutritional Pharmacology/Toxicology which uses high-information metabolomics workflows to identify metabolic targets associated with exposures. Using this information, nutritional interventions can be designed toward those targets to mitigate adverse effects or enhance positive effects. We also discuss the potential for this approach in precision nutrition where nutrients/diet can be used to target gene-environment interactions and other subpopulation characteristics. Deriving these "nutrient cocktails" presents an opportunity to modify the effects of exposures for more beneficial outcomes in public health.

Keywords: nutrition; pharmacology; toxicology; exposome; metabolomics; diet.

Introduction

Detrimental environmental exposures contribute to many acute and chronic diseases worldwide including cardiovascular disease, cancer, developmental, and neurological disorders, and many others. These exposures contribute significantly to worldwide mortality and have been an active area of study in biomedical fields. While traditional environmental health research was focused on the impacts of exposures to single agents or a few environmental factors, it is well-recognized that individuals are exposed to numerous environmental factors throughout their lifetimes and thus, research should shift towards studying the combined effects of all exposures. This led to the concept of the exposome, in 2005, which refers to the sum of exposures an individual experiences from conception onwards.[1] Individuals are exposed to different profiles of environmental compounds, which can lead to differences or similarities in health outcomes depending on the degree of overlap in chemical structure and biological activity of these compounds and the genetic makeup of the individual. Health outcomes related to exposures can also vary depending on the timing of the exposure during the life course. Accordingly, this concept also highlights that multiple early-life exposures explain health consequences that emerge many years later.[2]

The exposome concept was further defined in 2012 by categorizing exposures into three major domains: internal, specific external, and general external.[3] Internal exposures are processes occurring within the body such as metabolism, endogenous circulating hormones, body morphology, microflora composition/activity, inflammation, lipid peroxidation, oxidative stress, and aging. Specific external exposures refer to factors that have historically been major focuses of epidemiological studies linking exposure to health risks such as radiation, infectious agents, chemical contaminants/environmental pollutants, diet (eg, Mediterranean, nutrients, supplements, natural products), lifestyle factors (eg, tobacco, alcohol, drugs of abuse, physical activity), as well as occupational and medical interventions. Lastly, general exposures include broader social, economic, or behavioral/psychological factors such as social capital, education, financial status, psychological and mental stress, urban–rural environment, and climate. These domains form a picture of the entirety of exposures an individual may face. This socio-ecological framework that is built upon the exposure paradigm is referred to as the public health exposome.[4] It should also be noted that exposures in different domains may be intercorrelated, and exposure to factors in one domain may modulate the effect of an exposure in a different domain.

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Specific external exposures, especially environmental chemicals, are one of the most well-studied aspects of the exposome, as many compounds have defined biochemical mechanisms by which they interact with organisms to exert toxicological effects. Indeed, environmental toxins/toxicants participate in covalent and/or noncovalent interactions with host macromolecular structures (eg, receptors, enzymes, nucleic acids) to exert their mechanism of action, often leading to detrimental health effects.[5] Moreover, advancements in precision medicine/therapeutics indicate that individuals respond differently when exposed to the same chemical agents. The toxicodynamic and the toxicokinetic (absorption, metabolism, distribution, and excretion [ADME]) profile of a toxin/toxicant depends on various factors including genetic polymorphisms, gene expression, epigenetic profiles, comorbidities, co-exposures, biological/chronological age, microbiome composition, inflammatory status, gender/sex, and behavioral factors (stress, exercise, diet).[6-11] Notably, beneficial exposures (eg, prescribed drugs) also exert their biological effects through many of these mechanisms.[12] Two major barriers to understanding these dynamics are the large, continually growing number of environmental compounds for which little is known and the fact that what we do know comes from studying exposures in isolation, which does not reflect the reality of exposures in populations. This highlights a need to 1) conduct large-scale exposome studies to identify human population exposure profiles, 2) use high-throughput techniques (omics technologies) to understand how these exposome profiles alter human biology, and 3) use this information to guide the creation of potential intervention strategies to modify the effects of exposures while recognizing that reducing or removing harmful exposures should first be attempted if possible. Large-scale efforts supported by NIH such as the Children's Health Exposure Analysis Resource (CHEAR) and the Human Health Exposure Analysis Resource (HHEAR) aim to enhance our understanding of how exposures affect populations by providing researchers access to comprehensive exposure analysis tools, including mass spectrometry-based profiling of all small molecules (untargeted exposomics analysis), to add or expand environmental exposures to their health study.[13,14] Our question is: how can this information be used to design intervention methods to modify the effects of exposures?

An answer to this question may lie in nutrition. As evidenced by HHEAR and CHEAR studies, exposure to environmental chemicals has significant effects on the metabolome,[15-19] suggesting biochemical mechanisms are involved in the toxicological effects of these compounds. This is also the case for beneficial exposures (drugs) where the metabolome is increasingly being recognized as a readout for drug activity and efficacy.[12] Therefore, modifying these metabolic perturbations may provide a strategy to mitigate/prevent adverse health outcomes or enhance beneficial health outcomes related to exposures (Figure 1). Nutrients directly incorporate into metabolic pathways (eg, substrates, products, co-factors, and regulatory elements) and participate in key biological processes (eg, gene transcription, DNA methylation, DNA synthesis/repair, protein synthesis/transport, hormonal signaling),[20] thus dietary interventions may provide an effective means to counteract harmful metabolic imbalances caused by exposures to chemicals. Moreover, this provides a logistical advantage as exposure to environmental chemicals can be episodic and/or chronic. Therefore, an intervention strategy is needed that can be implemented consistently to at-risk individuals for disease (such as those with a known genetic variant, geographical location, or socioeconomic status that is known to associate with a disease outcome). It should be noted that the primary intervention for protecting against detrimental exposures is exposure reduction, however this is not always feasible for all individuals. In these instances, developing interventions to combat harmful exposures (eg, through nutrition) would be valuable alternative solutions if proven effective. Dietary modifications or nutrient supplementation are relatively safe to implement and can be tailored to an individual's preferences to make the intervention more palatable and increase adherence. In this concept manuscript, we provide evidence in support of a "Nutritional Pharmacology/Toxicology" approach which uses metabolomics—alone or in combination with other high information data streams—to identify metabolic perturbations associated with exposures and uses this information to develop nutritional interventions to enhance positive exposure-associated effects (eg, prescription drugs) or mitigate negative exposure-associated effects (eg, environmental contaminants). Notably, the term "Nutritional pharmacology" was used in 1980 in a letter to the editor in *The American Journal of Clinical Nutrition* which stated that nutrients could be used in high concentrations to provide therapeutic effects beyond supplying essential nutrients.[21] Herein, we expand upon this concept by using metabolomics technologies for the rational development of nutrient-exposure combinations. Additionally, we also offer perspectives of the importance of exposome research in health disparities/precision research through identifying nutritional needs for subpopulations and the role of nutrients in gene-environment interactions.

In certain contexts, nutritional and/or dietary factors have been demonstrated to protect against detrimental exposures or enhance beneficial exposures at the population level

To support this concept, one important question to address is: have nutrients and/or dietary patterns been shown to protect against environmental exposures in humans? Herein, we provide examples in the literature of nutritional/dietary interventions in human subjects protecting against the toxic effects of environmental exposures in certain contexts. Our focus is on studies that support nutrients targeting metabolic perturbations caused by exposures to exert protective effects. Notably, nutrients/dietary components protect against exposures by other mechanisms including altering ADME properties by acting as binding agents to prevent intestinal absorption of toxins/toxicants or to chemically modify toxins/toxicants prior to exposure to neutralize their toxic effects.[21,22] Additionally, dietary interventions reduce the amount of exposure to toxins/toxicants, particularly when oral ingestion of the chemical agent in food is a major route of exposure.[23] While these are important aspects to consider in the interplay between nutrition and the exposome, they are not the focus of this narrative. Lastly, to most efficiently demonstrate the translatability of the nutritional pharmacology/toxicology concept in exposome research, we focus solely on studies dealing with human subjects. Numerous studies have evaluated the modulatory effects of nutrients/dietary components toxins/drugs using *in vitro* and *in vivo* models and have proposed potential mechanisms for these effects. Readers are encouraged to view the numerous review articles summarizing these studies which are published elsewhere.[24-27]

While the number of human dietary intervention studies to protect against environmental exposures is sparse, there are instances in the literature that have demonstrated this principle,

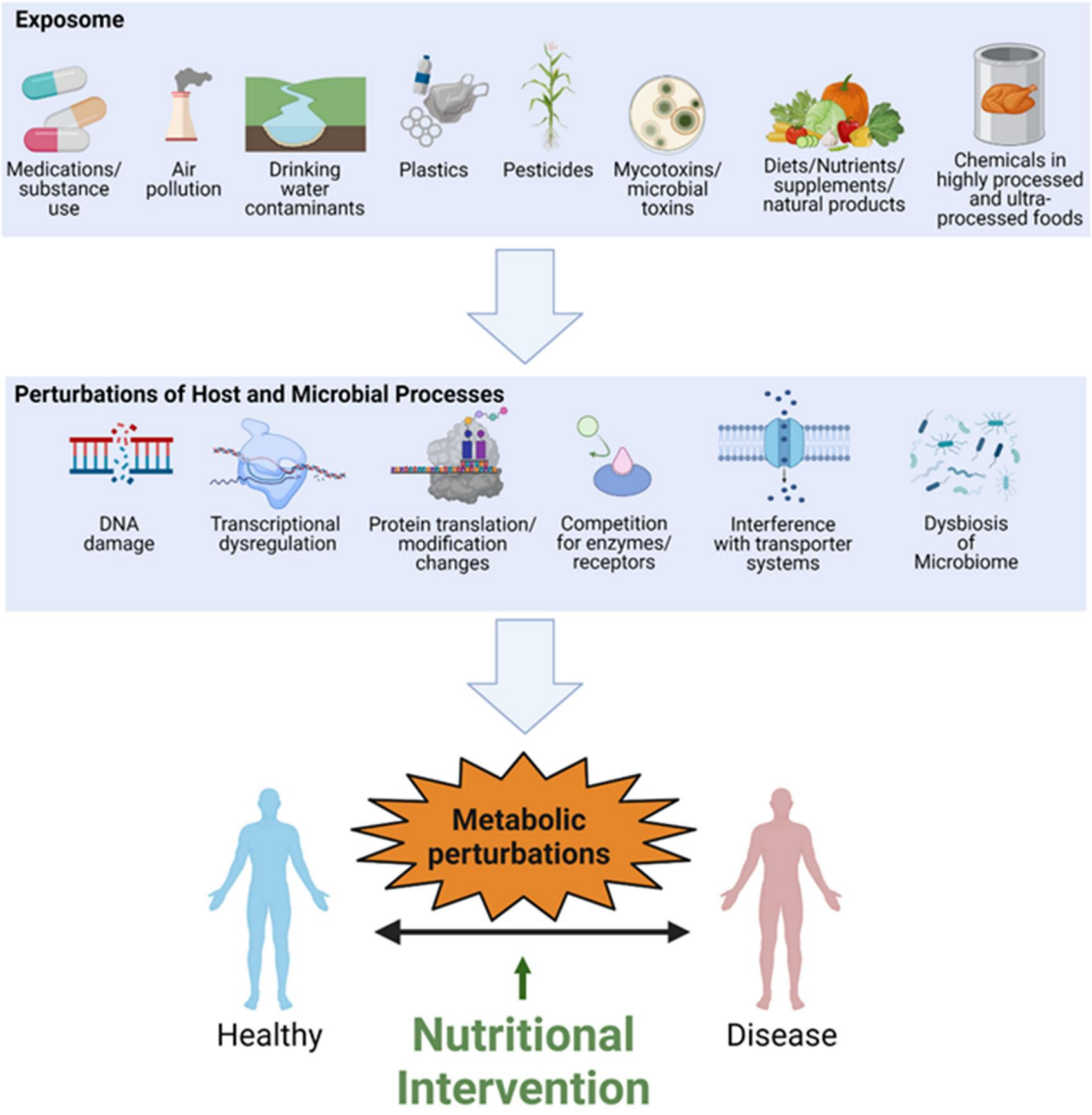

Figure 1. Schematic representation of the concept of nutritional pharmacology/toxicology in exposome research. Chemical agents that contribute to the exposome are composed of a diverse set of compounds including, but not limited to, medication/substance use, air pollution, drinking water contaminants, compounds from plastics, pesticides, mycotoxins/microbial toxins, and diet/diet constituents. Many of these compounds have been shown to affect a wide range of host biological processes which manifest as metabolic perturbations which can be detected with metabolomic technologies. These metabolic perturbations facilitate the transition from a healthy to a disease (eg, toxins/toxicants) phenotype, or a disease to a healthy (eg, medications/nutrients) phenotype. Nutritional intervention may provide a strategy to promote a healthy phenotype by either counteracting metabolic perturbations of detrimental substances or by enhancing metabolic perturbations of beneficial substances.

particularly using folate, polyunsaturated fatty acids (PUFAs), and antioxidants including polyphenols and vitamins C and E.[26]

Folate (vitamin B9) is an essential nutrient and co-enzyme that transfers one-carbon units. It regulates metabolic processes such as purine and pyrimidine synthesis and methylation reactions, and it is known to play a role in preventing neural tube defects.[28] Gaskins et al. investigated the effects of folate supplementation on counteracting the developmental and reproductive toxicity of air pollution (nitrogen dioxide [NO_2], ozone, fine particulate, and black carbon concentrations) in women using assisted reproductive technology. NO_2 exposure was associated with lower rates of live birth for women consuming $<800\,\mu g\,day^{-1}$ of supplemental folate, but women consuming $>800\,\mu g\,day^{-1}$ of supplemental folate did not have this negative association.[29,30] These findings suggest that supplemental folate intake may protect against the reproductive toxicity of air pollution. Folate also protects against endocrine disrupting compounds. Ormond et al. observed that occupational exposures to phthalates and hair spray during pregnancy led to increased risk of hypospadias, which was reduced with folate supplementation.[31] Notably, there have been randomized controlled trials showing increased arsenic excretion with folic acid supplementation, providing strong evidence for exposure protection with this nutrient.[32,33] These studies demonstrate that folate supplementation may have potential uses for public health in protecting against exposures related to developmental/reproductive toxicity.

PUFAs are a class of unsaturated fatty acids that contain more than one double bond in their carbon backbone and have an especially high prevalence in Mediterranean diets and in foods such as walnuts, fish, and sunflower seeds. Included in this class are omega-3 and omega-6 fatty acids which are known for their roles as signaling molecules and regulators of inflammation,

with omega-3 PUFAs generally regarded as beneficial due to anti-inflammatory effects and omega-6 PUFAs generally regarded as detrimental due to pro-inflammatory effects.[34] Importantly, these diets also contain high levels of monounsaturated fatty acids (MUFAs) and polyphenolics which contribute to health benefits associated with this dietary pattern.[35] Multiple studies have shown that PUFAs, or diets high in PUFAs, protect against the toxicological effects of air pollutants. Brigham et al. investigated whether dietary omega-3 or omega-6 intake modulated asthma outcomes in children following exposure to indoor particulate matter (PM). Results showed that higher omega-6 intake amplified the effects of PM $\leq$2.5 μm while higher omega-3 intake reduced the effect of PMs.[36] Chen et al. observed the association of omega-3 intake on cardiovascular outcomes following PM and ozone exposure and found that higher omega-3 consumption was associated with reduced adverse cardiovascular outcomes (total cholesterol, von Willebrand factor, tissue plasminogen activator, fibrin degradation products, very-low frequency heart rate variability (HRV), high-density lipoprotein, serum amyloid A, soluble intracellular adhesion molecule) following both ozone and PM $\leq$2.5 μm exposure.[37] Lastly, Lim et al. observed that individuals exposed to higher levels of PM $\leq$2.5 μm had increased mortality risk for cardiovascular disease (CVD) and cerebrovascular disease (CER), and those exposed to higher levels of NO_2 had increased mortality risk for CVD. This study also showed that individuals with a higher alternative Mediterranean Diet Index (aMED) score—a 9-point scale that measures an adherence to a Mediterranean diet—had lower rates of these air pollution-related mortalities.[38] These findings support that high PUFA intake, particularly omega-3, may have a protective effect against air pollution-related health outcomes, although the contributions of other bioactive components of the Mediterranean Diet should not be ignored.

Dietary antioxidants (eg, polyphenolic compounds, carotenoids, and vitamin C/E) reduce cellular damage related to oxidative stress. They reduce reactive oxygen species (ROS) by participating in oxidation-reduction reactions or enhancing cellular antioxidant systems.[39] High serum carotenoid concentrations reduced the risk of polychlorinated biphenyl (PCB)-related development of type 2 diabetes in an analysis of the National Health and Nutrition Examination Survey (NHANES) 2003-2004 data.[40] Additionally, Nobile et al. showed that polyphenol-enriched supplements improved markers of pollution-induced oxidative stress and skin aging in a double-blind study.[41] Vitamins C and E also improve exposure-related health outcomes. Péter et al. reviewed numerous studies that investigated the modulatory effect of vitamins C and E, either alone or in combination, on the pulmonary/inflammatory effects of air pollution. The seven studies included in this review all reported some degree of a positive effect of vitamins E and/or C supplementation in protecting against air pollution toxicity.[42] Lastly, Heitzer et al. showed that vitamin C normalizes endothelial dysfunction in chronic smokers suggesting a potential role for antioxidant vitamins modifying the effects this exposure.[43] However, it should be noted that some studies have observed an increase in lung cancer incidence in smokers with supplementation of antioxidants such as beta-carotenes.[44] Therefore, more research is needed in this area to better understand how antioxidants modify the effects of smoking.

While nutrient-drug interactions have historically been viewed as negative, there's also evidence that has shown that nutrients can enhance the effects of beneficial exposures (eg, drugs) in human subjects.[12,45] For example, Liu et al. showed that supplementation with a low dose (60 mg) of caffeine increased the effectiveness of escitalopram (an antidepressant drug) in reducing depressive scores by nonpharmacokinetic means.[46] Multiple studies have shown that folate can increase the effectiveness of antidepressant medications. Godfrey et al. found that individuals who were folate deficient had an improved response to antidepression treatment if supplemented with 15 mg of folate daily. Interestingly, this effect became greater over time and was also shown to improve psychotropic treatment for schizophrenia.[47] In another study, Alpert et al. performed a study where 22 patients who only had a partial response or nonresponse to selective serotonin reuptake inhibitor (SSRI) therapy were augmented with 8 weeks of 15-30 mg day^{-1} of folinic acid (leucovorin). These individuals were observed to have a further improvement in depressive symptoms following this supplementation, with 19% of subjects experiencing remission.[48] Another study observed that folic acid supplementation enhances lithium prophylaxis of bipolar and unipolar disorders. The study found that individuals with low folate levels experienced up to a 40% reduction in their affective morbidity following folate supplementation and subsequent increase in plasma folate levels.[49]

Other examples of beneficial nutrient-drug interactions include calcitriol and androgen-independent prostate cancer (AIPC). Beer et al. observed that five AIPC patients who completed an 8-week cycle of oral calcitriol administration (0.5 μg kg^{-1}) had to a 50% reduction in prostate-specific antigen (PSA) in APIC after taking intravenous docetaxel.[50] This was supported by a follow-up study which used a similar dosing regimen in 37 patients where 81% showed a positive response in PSA levels with 59% of patients showing a >75% reduction in PSA levels.[50] Another well-studied, positive drug-nutrient interaction in oncology treatment is the combination of leucovorin (folinic acid) and 5-fluorouracil. This combination is commonly used to increase 5-FU efficacy, in addition to oxaliplatin, in the treatment of colorectal cancer, and is commonly referred to as the FOLFOX regimen.[51,52] Vitamin D has been shown to increase the effectiveness of therapies in infectious diseases (hepatitis C, tuberculosis), osteoporosis, epilepsy, atopic dermatitis, multiple sclerosis, and chronic kidney disease.[53] In a study by Liso et al., 47 patients with inflammatory bowel disease, Chron's disease, and ulcerative colitis taking infliximab were enrolled in a study where 20 individuals received a purple corn supplement with a high anthocyanin content, and 27 individuals did not. Results showed that individuals taking the antioxidant-enriched purple corn supplement showed an improvement in inflammatory markers compared with individuals who did not take the supplement.[54] Taken together, these studies demonstrate that beneficial drug-nutrient interactions have been seen in clinical settings. It should be noted that more research is needed to better understand the mechanisms that underlie these beneficial interactions, and more drug-nutrient interactions need to be studied.

Metabolomics workflows can be used to identify perturbations associated with exposures

The above studies support the concept that nutritional interventions may provide a promising approach to modulate the health effects of exposures; however more in-depth research is needed. For example, assessing the exposome of individuals as there are likely multiple co-exposures occurring in study participants that may confound or complicate results. Additionally, high

information workflows are needed to understand how exposures modulate metabolism so that interventions can be designed to modify these effects. The example studies provided above were based on known associations with pre-formulated hypotheses. The Nutritional Pharmacology/Toxicology workflow does not depend on known associations, but rather uses metabolomics technologies to identify metabolic perturbations and their associations with exposures to derive nutritional interventions. Metabolomics has emerged as a high-throughput, high-dimensional tool to discover how low molecular weight (<1000 Da) metabolites of the host system associate with the onset, severity, or progression of disease, or the response to therapeutic intervention.[55] In the field of nutrition, early efforts applied metabolomics to investigate the metabolic response of the host system to specific nutrients, dietary intake, and weight status.[56] In the field of pharmacology and toxicology, studies evaluated the response of host metabolism to drugs and chemicals to gain insights into mechanisms and perturbations in target organs.[57,58] We posit that the field is ready to combine these efforts, making connections between nutrients and exposures (toxins, drugs, etc.) through their effects on metabolic processes.

Recent technological advancements have led to the simultaneous detection of tens of thousands of features in commonly accessible biospecimens (urine, blood, stool, etc.), many of which are not readily identifiable/annotatable to known compounds giving rise to the concept of metabolomics "dark matter".[57,59] Over the past decade, knowledge bases have rapidly expanded and contain a high amount of spectral data and data mining tools to improve signal annotation and expand the definition of an individual's metabotype.[60] Although many of the signals remain unknown, high resolution mass spectrometry metabolomics affords the simultaneous detection of endogenous metabolites as well as exogenous metabolites produced by microbial systems, ingestion of foods and beverages, use of drugs, medications, caffeine, and tobacco, exposures to household or industrial chemicals, as well as automobile and industrial emissions.[61] Because of this, metabolomics technologies are well-positioned to make connections between endogenous metabolites and exposures.

Figure 2 presents a general workflow whereby differential metabolic profiling of exposed and nonexposed individuals is performed to determine metabolic perturbations caused by toxins/toxicants. Because metabolomics workflows can detect exposome compounds, prior knowledge of exposure history is not needed. Rather, individuals can be classified as exposed or nonexposed post-analysis based on the detection of exposome compounds in the metabolomics method. This is particularly useful in large cohorts where the number of exposed individuals can reach large enough sample sizes for downstream analyses. Examination of metabolic perturbations can point to nutritional interventions to target metabolites and/or metabolic pathways to potentially prevent or mitigate toxic effects associated with the exposure. This paradigm can also be applied to beneficial exposures (eg, prescribed drugs and health-promoting phytochemicals in the diet) to compose nutritional interventions to enhance the health effects of a therapeutic substance. Importantly, because exposures target multiple metabolic pathways, these nutritional interventions should be designed to include multiple nutrients with multiple metabolic targets. Generating these "nutrient cocktails" has recently been proposed in some of our recent studies. In a study of osteoarthritis (OA), the metabolic profiles of obese individuals diagnosed with OA were compared with profiles of obese individuals diagnosed as not having OA. This study demonstrated a decrease in the short chain fatty acids propionate that is produced by gut microbes (eg, clostridia) and related to the amount of indigestible fiber in the diet, a decrease in glucosamine derived metabolites, and perturbations in leukotriene metabolism that can be related to the precursor PUFAs. A nutrient cocktail or diet controlling the ratio of omega-3/omega-6, and increased glucosamine, and short chain fatty acids was suggested as a potential intervention strategy to mitigate inflammation associated with OA, although this would need to be tested in future studies.[62] In a study of opium use disorder (OUD), metabolic profiles of opium users (some diagnosed as OUD positive) were compared with the profiles of individuals reporting never using opium. This study demonstrated general metabolic disruptions in neurotransmitter metabolism, Krebs cycle, sugar metabolism, fatty acid metabolism, and one carbon metabolism, and a higher level of phthalates and volatile organic compounds in urine of the opium users. This study led to the conclusion that a nutrient cocktail composed of vitamins, vitamin-like compounds, fatty acids, and sugars may mitigate the onset or severity of addiction.[19] This concept of deriving nutritional cocktails based on metabolomics analysis that we have presented is still in the early stages and much more research is needed to better understand the potential of this approach.

Health disparities and gene-environment interactions: the potential to generate precision nutrition interventions for different subpopulations

Another important factor to consider when investigating nutrients to combat exposures are differences within subpopulations. There are significant health disparities across subpopulations regarding environmental exposures—race, sex, and other social determinants of health (eg, healthcare access and quality, food access and quality, education access and quality, social and community context, economic stability, and neighborhood and built environment) that play significant roles in the types and amounts of exposures an individual may experience.[63-65] Even when exposed to the same chemical agent at the same level, many of these factors may cause an individual to have a more severe response to the exposure than another. As such, exposome studies are needed that assess subpopulation differences in exposure profiles as well as differences between subpopulations in metabolic disruptions following the same exposure. With this information, exposome measurements have the potential to be used for precision therapy approaches by which an individual's demographic information and exposure profile can be used to determine tailored nutritional interventions to maximize health benefits.

The importance of personalizing nutritional interventions to combat adverse effects of exposures is further demonstrated by the concept of gene-environment interactions. Gene-environment (GxE) interactions refer to the interplay between the genetic makeup of an individual and the physical and social environments resulting in a specific phenotype[66] (Figure 3A). One example of this is the association with N-acetyltransferase 2 (NAT2) polymorphisms with increased risk of bladder cancer in individuals who were current smokers or who had occupational exposure to arylamines (including jobs in rubber/chemical industries which have high exposure to these compounds). NAT2 is a xenobiotic biotransformation enzyme which catalyzes acetylation reactions and it is important for clearing carcinogens such as arylamines and other tobacco constituents. A significant association was found between NAT2 variants leading to slower

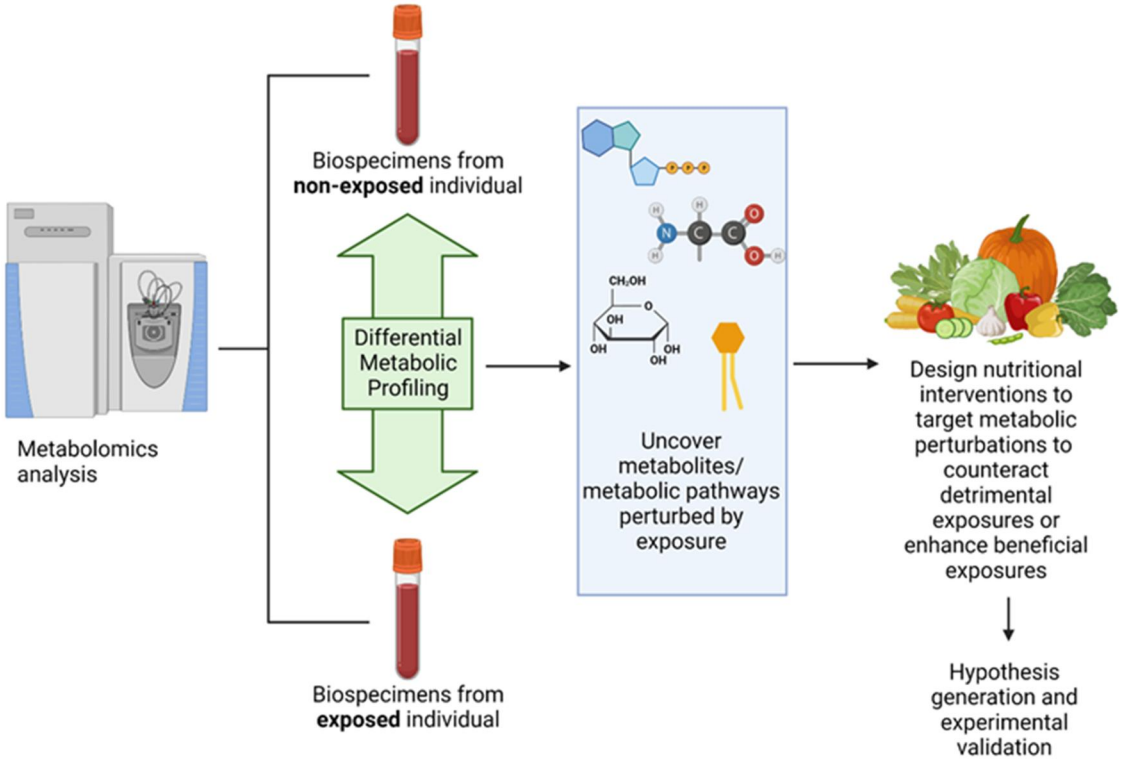

Figure 2. Metabolomics technologies allow for the design of nutritional interventions to modulate the effects of exposures. Differential metabolomic profiling on biospecimens from exposed and nonexposed individuals identifies metabolites and metabolic pathways affected by exposures, both detrimental and beneficial. Nutritional interventions can then be designed to target these metabolites/metabolic pathways and can be evaluated in controlled experimental models to assess for protection against the toxicological effects or enhancement of the pharmacological effects of the exposure.

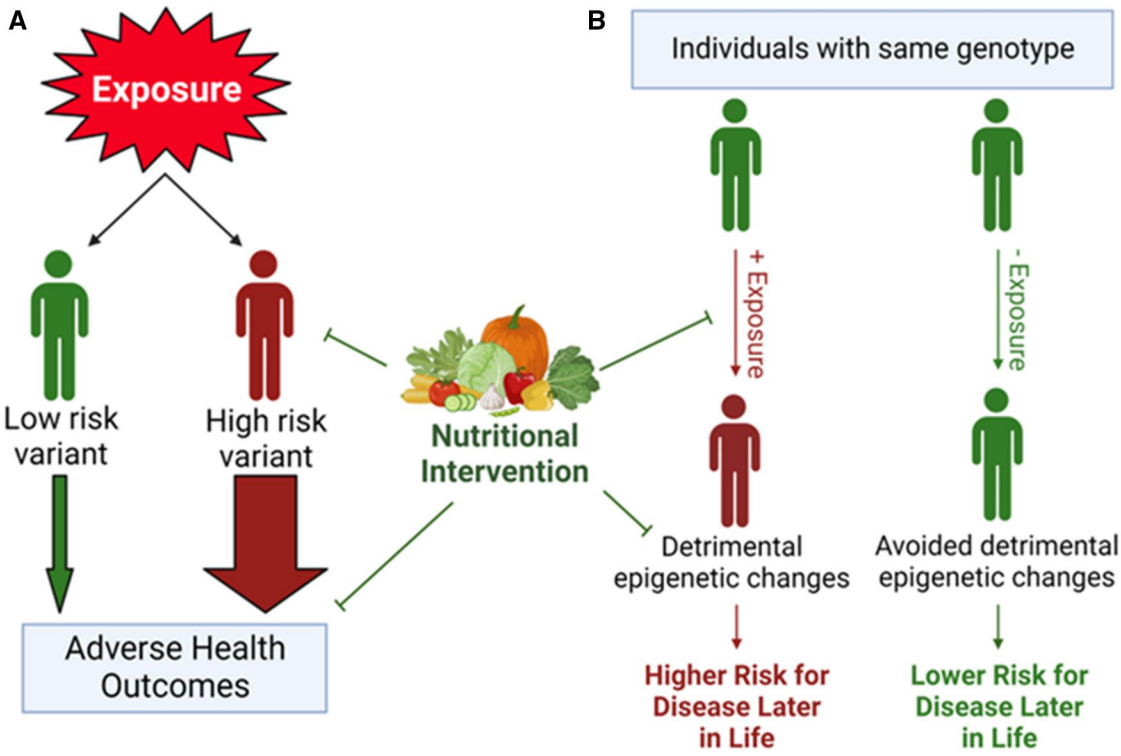

Figure 3. Nutritional interventions may provide a precision therapeutic approach to augment gene-environment interactions. Gene-environment interactions fall into two major categories: (A) Two individuals exposed to the same exposure can have different health outcomes due to the presence of low or high risk genetic variants, and (B) two individuals with the same genotype can have different exposure profiles which leads to differences in epigenetic changes resulting in different health outcomes later in life despite the same underlying genotype. Nutritional interventions can be used as a precision therapy to aid those with high-risk genetic variants or to mitigate/reverse adverse epigenetic changes caused by exposures.

acetylation rates and bladder cancer in current smokers and those with occupational exposure to arylamines.[67] Another example is with variants in the Glutathione S-transferase P1 (GSTP1) and microsomal epoxide hydrolase (EPHX1) genes and exposure to air pollution. EPHX1 and GSTP1 are involved in the metabolism of reactive polyaromatic hydrocarbons (PAHs) which are found in air pollution generated by combustion of fossil fuels and also in barbecued meat and cigarette smoke. Salam et al. showed that children with variants in GSTP1 and EPHX1 had an increased risk for developing asthma when exposed to traffic-related air pollution.[68] Another example comes from the relationship between paraoxonase 1 (PON1) polymorphisms and Parkinson's disease following pesticide exposure. PON1 encodes for an esterase/lactonase and it is able to hydrolyze organophosphorus compounds. Individuals with a polymorphism in PON1 had a faster progression of Parkinson's symptoms following exposure to organophosphate pesticides.[69] Finally, Merino et al. showed an added benefit of diet and physical activity on cardiovascular disease risk factors depending on an individual's generic risk profile for coronary artery disease.[70] Taken together, these examples demonstrate that gene-environment interactions play a large role in dictating one's response to exposures, and that individuals exposed to the same environmental insult may have drastically different health outcomes depending on their genotype. Currently, nutritional intervention approaches in these situations is lacking as is information regarding the optimal window for intervention, and metabolomic approaches may be able to help in filling these knowledge gaps to uncover potential strategies for further testing. Taken together, genetic variant information could one day be used to identify individuals with the highest need for intervention (eg, nutritional) to protect against the adverse health effects of exposures.

Another aspect of gene-environment interactions is that exposures can alter gene expression profiles through epigenetic changes. This is especially important when considering early-life exposures. Exposure to a toxin/toxicant at an early age (or during fetal development) can lead to persistent epigenetic changes which alter gene expression patterns, leading to a higher risk of developing adverse health outcomes later in life (Figure 3B). Notably, epigenetic patterns can be passed down from mother and to offspring, indicating that the effects of an individual's exposure in early life can be trans-generationally passed down.[71,72] In this way, environmental insults have lasting health impacts on multiple generations. For example, prenatal exposure to tobacco smoke is associated with increased risk of diseases later in life such as cancer and cardiovascular disease.[73,74] Accordingly, prenatal exposure to tobacco smoke alters global and gene-specific DNA methylation patterns which persist later in life, providing a mechanism for this increased disease risk.[75,76] Another example lies with early life exposure to heavy metals, particularly arsenic. Prenatal exposure to arsenic increases risk for developing cancer, cardiovascular disease, nonalcoholic fatty liver disease, and diabetes.[77] Alterations in DNA methylation in cord blood have been observed following arsenic exposure during pregnancy, which may explain the increased risk for chronic diseases.[78] This paradigm of early life exposures leading to chronic disease later in life is challenging to investigate—toxins/toxicants and their metabolites are often cleared from the body at the time of diagnosis, making it difficult to attribute the disease to exposures unless an individual is followed throughout their lifetime and currently, few intervention strategies (including nutritional) are available beyond exposure reduction strategies. More research is needed to identify epigenetic signatures associated with different exposures to better identify an individual's exposure history and how that relates to current/future health outcomes.

In both scenarios, nutritional intervention may play a role in mitigating adverse health effects due to gene-environment interactions (Figure 3). Individuals who have a genetic variant that increases disease susceptibility can be given stronger dietary recommendations to give increased protection against the metabolic perturbations caused by the exposure. Nutritional interventions may also aid in preventing epigenetic modifications if administered during the time of exposure. Furthermore, nutrition has been shown to alter the epigenome and may provide a mechanism to reduce or reverse existing epigenetic perturbations caused by exposures to mitigate disease risk.[79]

On the pharmacological side, our workflow could be used to investigate individuals who are responsive to beneficial treatments versus those who are nonresponsive or partially responsive (Figure 4). Understanding variations in treatment response has been an area of great scientific interest in many pharmacological settings.[80-85] Using metabolomics, responders and nonresponders for a pharmacological exposure can be analyzed to determine metabolic processes/networks that differentiate responder status. These results can be used to generate hypothesis regarding metabolic processes that can be targeted through nutritional interventions or other means to enhance responsiveness. Indeed, metabolomics approaches have been used in several pharmacological settings to identify differences in responders and nonresponders, indicating that responder status is often characterized by metabolic differences before, during, or after treatment.[86-90] This indicates that metabolomics can successfully identify biological differences linked to responder status which may potentially play a causal role in therapeutic response. We propose that this is an exciting future direction of pharmacometabolomics research and more efforts are needed to explore this area.

An additional internal interface that contributes to the exposome is the diet-gut microbiome axis. The microbiota that inhabit the intestine appear to confer beneficial or adverse effects to host physiology given the dietary context of which they are exposed. In the context of a high carbohydrate diet, they produce short chain fatty acids, by fermentation of indigestible fiber components, which promote colon health.[91] In other contexts, such as when faced with diets high in phospholipids, they have been found to produce metabolites such as trimethylamines that are processed by the host liver to generate metabolites, such as trimethylamine oxides, harmful to the cardiovascular system.[92] Similarly, other microbiota derived metabolites have been observed to be associated with many disease states.[93,94] A diverse or heterogenous population of the gut microbiota is generally seen as beneficial to the host, and dietary exposure appears to be one of the principal driving factors determining an individual's gut microbial composition.[95] Hence, the diet-gut microbiome axis presents as a potentially intervenable target to tailor favorable outcomes. It should be noted that this may also provide additional complexities or challenges for designing nutritional interventions. For example, Ke et al. demonstrated that dietary thymidine and serine enhance 5-fluoro 2'deoxyuridine (FudR) toxicity through different microbial mechanisms, suggesting that the microbiome can alter the response of the host to a drug without altering the drug or host.[96] The interaction of the microbiome and the exposome is complex and while it is not the topic of this article, this has been thoroughly reviewed elsewhere.[10,97] As more research is performed to study the interaction of nutrition

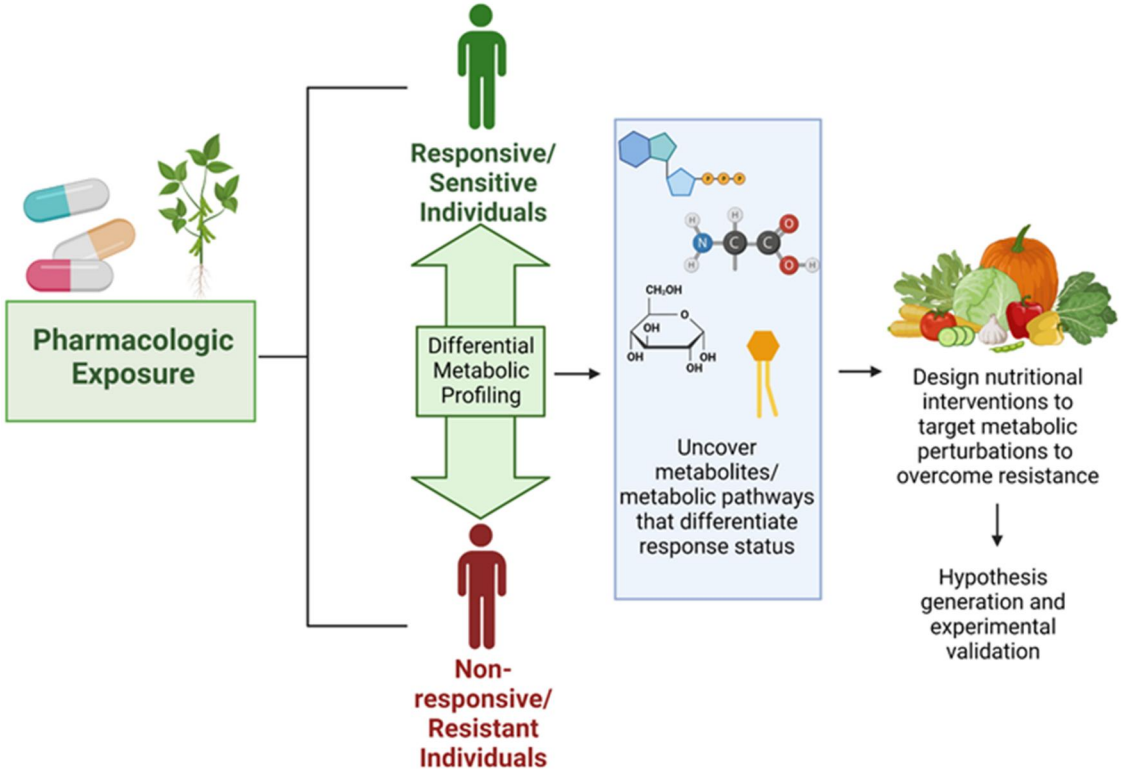

Figure 4. Metabolomics technologies allow for the design of nutritional interventions to overcome resistance to beneficial exposures. Differential metabolomic profiling on biospecimens from responsive/sensitive individuals and nonresponsive/resistant individuals receiving the same pharmacologic exposure (eg, drugs, natural products) can identify candidate metabolites and metabolic pathways to target to increase efficacy. This approach allows for the generation of hypothesis to target these metabolites and metabolic pathways to potentially enhance treatment outcomes.

and exposures, care should be taken to consider the effects of the microbiome in these studies.

In silico experimentation and hypothesis generation for exploring nutrient-exposure relationships

Above, we have presented a workflow to use metabolomics methods to better understand the biological perturbations of the exposome and to potentially derive hypothesis for nutritional intervention strategies. However, there are many additional factors to consider in exposome studies which can potentially be available including genetic information, partial/complete mechanistic disease information, dietary patterns, demographic information, etc. These other factors may provide additional information beyond metabolomics/exposomics data to derive optimal intervention strategies. Therefore, a more intensive framework may be needed to integrate these other data sources with metabolomics/exposomics data for this purpose, and would ideally be able to incorporate data across multiple exposomics studies to more clearly identify precision intervention strategies.

One existing challenge with integrating these types of data is a lack of common standards and terminologies across exposome studies. A few research programs have leveraged ontologies (computational terminology standards) to standardize environmental health or nutrition data to alleviate these challenges. Applying ontologies, the CHEAR and HHEAR programs integrate exposure data and associated health outcome data across multiple studies and make them available to the research community.[13,14] The FOODON ontology describes parts of animals, plants, and fungi bearing a food role.[98] However, these programs are rare examples of computable exposure and nutrition data and have not yet been integrated with other resources. The absence of machine-readable nutrition data is a major roadblock to discovering connections between diet and the environment, and limits the field's ability to derive nutritional intervention strategies to modulate the effects of exposures. Therefore, new approaches are needed to organize machine-readable data in a way that can be continually built upon as new data emerge.

A solution that we propose is the use of Knowledge Graphs (KGs). KGs and their underlying ontologies link information from different sources, similar to how people are linked in online social networking. Individuals who do not know each other are linked together via 'friends of friends' or 'common hobbies', etc. Similarly, a collection of partially overlapping data sets are combined into one large, interconnected data set (the KG) to answer complex questions that could not be answered before, thereby making data interpretation and hypothesis generation more comprehensive, easier, and faster. Using KGs for hypothesis generation (eg, drug repurposing) is an active area of research, with studies using a combination of manual exploration and automated link prediction.[99-101] Using the standards in KG-Hub,[102] improvements have been made in rare disease diagnosis within the Monarch Initiative,[103] which focuses on genotype-phenotype data. However, environmental factors, including diet, are not yet available within the Monarch KG. Recently, landscape assessment of nutrition resources was performed to enhance ontologies and KGs for health interpretation of dietary risk factors as well as mechanistic discovery.[104] Incorporation of knowledge from the Comparative Toxicogenomics Database (CTD)[105]—a manually curated database about chemical–gene/protein interactions, chemical–disease, and gene–disease relationships, the

OSU/PNNL Superfund Research Program Analytics portal (SRP),[106] the Micronutrient Information Center (MIC)[107]—a freely available, evidence-based resource on the role of nutrients and dietary factors in health and disease, among other sources, would greatly enhance computable knowledge of dietary and environmental health. Combining these data into a single, query-able graph would allow for the discovery of deep connections in the molecular processes that are affected by environmental exposures and nutrients (Figure 5). Metabolomics data, particularly from large-scale cohorts like those analyzed in HHEAR and CHEAR, can also be integrated into these KGs to better understand the link between metabolic perturbations, exposures, and other individual/population data—including dietary information—to better understand the relationship between nutrients and these other factors. Advantages of using KGs over other strategies includes: 1) semantic integration—KGs utilize ontologies and semantic relationships to integrate diverse datasets, drawing connections between different elements (eg, exposures, nutrients, health status, etc.) in a comprehensive analysis of data with enhanced visualization capabilities; 2) flexibility and scalability—KGs are able to easily accommodate new data sources, expand analysis scopes, and incorporate emerging knowledge to ensure analyses are kept up-to-date and comprehensive; 3) data exploration capabilities—KGs allow researchers to explore known and unknown deep connections for hypothesis generation, accelerating the discovery process including potential intervention strategies for testing; and 4) interoperability and collaboration—KGs promote data analyses across different research domains, bridging gaps between fields of study and enabling multidisciplinary research which would aid in a better understanding of the exposome and its impact on human health. A disadvantage of this approach is the necessity for unified ontology systems to facilitate data merging but as mentioned above, the exposomics field is moving in this direction which will help in overcoming this barrier. The use of KGs for hypothesis generation has great potential to accelerate the scientific process, but only if we develop repeatable, reliable methods for building KGs and using evidence to iteratively improve them. This has rarely been done in the past, and never by using dietary or environmental data. This approach would greatly increase the value of metabolomics data in exposome studies, allowing for deeper connections to be made between metabolic perturbations of exposures and more comprehensive hypothesis generation for intervention strategies.

Conclusion

In conclusion, the exposome describes the totality of exposures individuals face across their lifetime and has complex effects on human health. Much of the effects of the exposome remain unknown as the majority of studies have focused on one or a small number of exposures. Regardless, the link between environmental chemical exposure and human health is clear, and interventions are needed to reduce or prevent exposure-related adverse health outcomes. High information workflows using metabolomics technologies can capture the metabolic perturbations caused by exposures and reveal novel mechanisms by which these compounds modify health outcomes. Revealing how these imbalances are related to our essential nutrients can point to nutritional targets to inform the development of intervention strategies. Herein, a concept of nutritional pharmacology/toxicology has been proposed to target these metabolic perturbations as a method to combat the adverse effects or enhance the beneficial effects of these compounds. This method not only has potential to be applied generally across populations, but it may also be used as a precision public health approach to target subpopulations based on race, sex, social determinants of health, responder status, genetic variants that predispose one to the exposure, or towards epigenetic perturbations that have resulted from prior exposures. Similar to drug development paradigms that use combination cocktails of drugs to hit multiple therapeutic targets,[108-110] it is likely the field of nutrition will evolve to evaluate an individual's exposure profile, metabotype, and genotype to derive combination cocktails of nutrients to return an

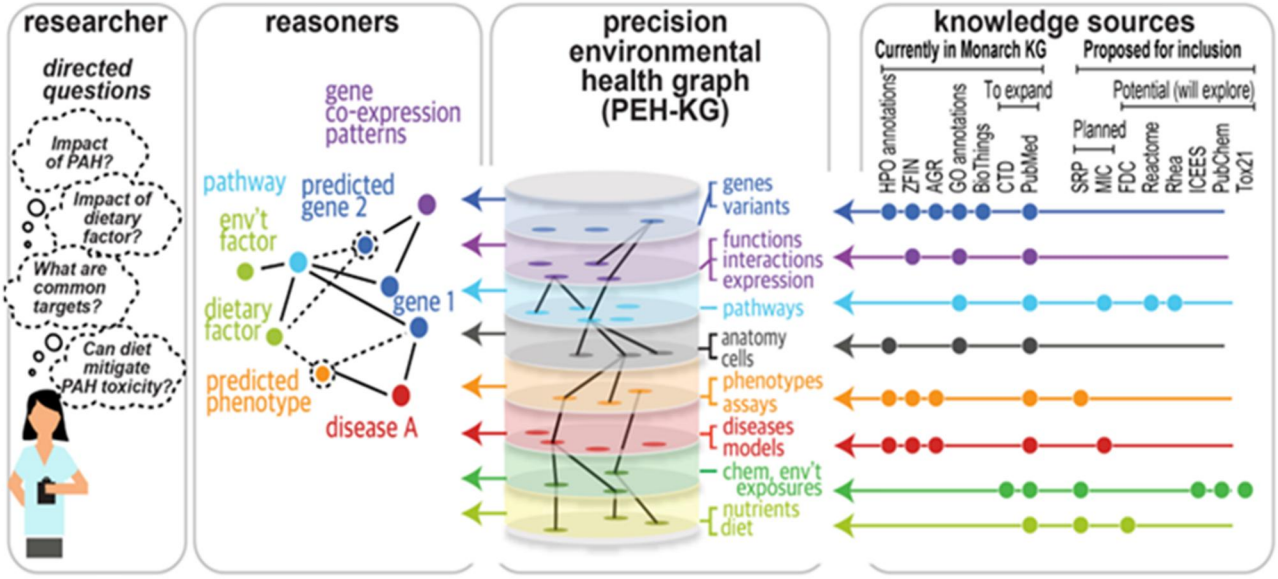

Figure 5. ETL pipeline to transform source data into a single, query-able Knowledge Graph. Existing Monarch Initiative Infrastructure (Koza and KGX) will be leveraged to create a pipeline to map knowledge sources to ontologies and Biolink to enable integration of heterogeneous data across scale and modality (PEH-KG) in a structure that allows for reasoning (eg, link prediction) and researcher questions through a Neo4J graph database query endpoint. AGR Alliance of Genome Resources,[111] BioThings,[112] FDC Food Data Central,[113] Reactome,[114] Rhea,[115] ICEES Integrated Clinical and Environmental Exposures Service,[116] PubChem,[117] Tox21.[118]

individuals' metabolic imbalance to their normal state. To fully study these factors, better experimental models are needed for exposome research and related interventions to make translatable discoveries. Also, much of the current work regarding nutrient-toxin and nutrient-drug interactions (including those presented above) focuses on generic targets such as oxidative stress, inflammation, or endothelial function as targets of nutrients rather than specific metabolites or metabolic processes. Therefore, more research is needed to better understand how nutrients target specific metabolic processes to modify an individual's response to toxins or pharmacological agents. Additionally, more research is needed where exposures (both toxins and drugs) are studied as mixtures rather than single agents to reflect exposure profiles seen in populations, ideally in the presence or absence of select nutrients to better understand nutrient-environment interactions. Lastly, a better understanding of the clinical effectiveness of altering metabolism in these approaches is needed to better understand the utility of these approaches. Some barriers—including variability in metabolomics assays, lack of standardized data analytical approaches for mixtures, inadequate sample sizes, potential unintended consequences of food/supplement interventions—stand in the way of the widespread adoption of this concept. However, ongoing efforts in the metabolomics community for standardization practices and large metabolomics/exposomics consortium efforts such as HHEAR and CHEAR will aid in alleviating these issues. Advancements in these areas will aid in the development of nutritional interventions for public health and precision interventions to modify the effects of exposures.

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Author contributions

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Data availability

No original data was produced for this manuscript.

Conflict of interest statement

None declared.

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