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Systems Epidemiology: A New Direction in Nutrition and Metabolic Disease Research

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Abstract Systems epidemiology applied to the field of nutrition has potential to provide new insight into underlying mechanisms and ways to study the health effects of specific foods more comprehensively. Human intervention and population-based studies have identified i) common genetic factors associated with several nutrition-related traits and ii) dietary factors altering the expression of genes and levels of proteins and metabolites related to inflammation, lipid metabolism, and/or gut microbial metabolism, results of high relevance to metabolic disease. System-level tools applied type 2 diabetes and related conditions have revealed new pathways that are potentially modified by diet and thus offer additional opportunities for nutritional investigations. Moving forward, harnessing the resources of existing large, prospective studies within which biological samples have been archived and diet and lifestyle have been measured repeatedly within individuals will enable systems-level data to be integrated, the outcome of which will be improved personalized *optimal* nutrition for prevention and treatment of disease.

Keywords Nutrition · Systems · Genomics · Transcriptomics · Proteomics · Metabolomics · Type 2 diabetes · Obesity · Metabolic disease · Epidemiology · Populations · Diet · Network · Nutrigenetics · Nutrigenomics

Introduction

Traditional epidemiology has made important contributions to the identification of many key lifestyle and environmental risk factors for chronic disease. Technical advances that now allow high-throughput measurements of genomic, transcriptomic, proteomic, and metabolomic traits in combination with more sophisticated bioinformatics and statistical methods provide epidemiologists an unprecedented opportunity to unlock the full potential of their research approach. "Systems Epidemiology" couples traditional epidemiologic methods with modern high-throughput technologies to enhance biological understanding of metabolic pathways in humans [1–4]. Nutrition research is a potentially ideal field for the application of systems approaches [5]. The dietary record and food frequency questionnaire have been instrumental to developing knowledge of the role diet plays in population health. However, these tools along with other aspects of epidemiological methods have well-known limitations that impede further advancements in the human nutrition field. Foods are mixtures of known and unknown constituents, and separating as well as characterizing the effects each in the context of individual intrinsic variances is an ongoing challenge in classical nutritional epidemiology.

The purpose of this review is to provide an overview of systems epidemiology with application to nutrition. We discuss progress in applying system-level tools to the study of both type 2 diabetes (T2D) and nutrition. Results of each highlight important connections between them and underscore the great potential for systems epidemiology in advancing nutrition research for disease prevention.

System Level I: Human Genome

Enthusiasm for systems epidemiology is fueled, in part, by the marked recent successes in human genomics: the study of an individual's entire gene set, including gene-gene and gene-environment interactions. Genome-wide association studies (GWAS) of T2D have contributed to the identification of approximately 65 susceptibility loci [6••], which is an astounding improvement upon the small handful of loci described pre-GWAS [7]. Genome-wide analytical approaches also have proven successful for a number of important nutrition-related traits (Table 1). For example, single nucleotide polymorphisms

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Table 1 Genome-wide significant loci associated with nutrition-related traits[1]

Trait	Locus[2]	Genes in region	Ref
Plasma amino acids			
Alanine, isoleucine	2p24	*GCKR, SNX17, PMG1, NRBP,FNDC4*	[135]
Glutamine	10q24	*HOGA1, MORN4*	
	12q13	*TIMELESS, MIP, SPRYD4, GLS2, BAZ2A*	
Histidine	4q35	*CYP4V2, KLKB1, F11*	
Phenylalanine	5q33-q35	*F12, GRK6*	
Tyrosine	16q22	*CHST4, TAT, PHLPPL, MARVELD3, AP1G, SNORD71, ZNF821, PKD1L3*	
Valine	2p15-p13	*SLC1A4*	
	4q22	*PPM1K, HERC6, ABCG2*	
Betaine	12p13.33	*SLC6A12, SLC6A13*	[136]
	5q14.1	*BHMT, BHMT2, DMGDH*	
Glycine	2q34	*CPS1*	
Serine	1p12	*PHGDH*	
Plasma fatty acids			
Linoleic acid, omega-3 FA	11q12-q13	*MYRF, FEN1, FADS(1–3), DAGLA, BEST, FTH1*	[135]
Linoleic acid omega-6 & omega-7 FA	11q23	*BUD13, ZNF259, APOA5, APOA4*	
	1p31.3	*DOCK7, ANGPTL3*	
Linoleic acid, omega-6 & omega-7 FA, omega-9 & saturated FA, other PUFA than linoleic	15q21-q23	*LIPC, ADAM10*	
Omega-9 & saturated FA	2p24	*GCKR, SNX17, PMG1, NRBP1, FNDC4,*	
Other PUFA than linoleic	11q12	*CD6, CD5, VPS37C, PGA3*	
Plasma vitamins & minerals			
Beta-carotene	16q23.2	*PKD1L2, BCMO1*	[137]
Calcium	3q21.1	*CASR,CSTA,WDR5B,KPNA1,CCDC58*	[138, 139]
Carbohydrate-deficient transferrin (and %), transferrin, total iron binding capacity	3q22.1	*TF, SRPRB*	[140–143]
Carbohydrate-deficient transferrin (%)	1p31	*PGM1,RPL19P3*	[140]
Erythrocyte mean cell volume, iron-soluble transferrin receptor	22q12.3	*TMPRSS6*	[143–146]
Erythrocyte mean cell volume, ferritin, iron, soluble transferrin receptor, transferrin, transferrin saturation, unsaturated iron binding capacity, total iron binding capacity	6p21.3	*HFE*	[140–144, 146]
Ferritin	6p22.2	*SLC17A1*	[143]
Soluble transferrin receptor	11q23	*BUD13, ZNF259, APOA5, APOA4*	[146]
	11q23.3	*PCSK7*	
Transferrin saturation	6p22.1	*HIST1H2BJ, VN1R13P, VN1R11P*	[142]
Magnesium	11p14.1	*DCDC5, MPPED2*	[147]
	12q21.33	*ATP2B1, MRPL2P1*	
	1q22	*MUC1*	
	3q26.2	*MDS1, MECOM*	
	4q21.1	*SHROOM3*	
	9q21.13	*TRPM6*	
Retinol	10q23.33	*RBP4, FFAR4*	[148]
	18q12.1	*TTR,B4GALT6*	
Vitamin B12	11q12.1	*MS4A3*	[149–151]
	13q32.3	*CLYBL*	
	19p13.3	*FUT6*	
	19q13.33	*FUT2*	
	5q32	*ASS1P10, PRELID2*	

Table 1 (continued)

Trait	Locus[2]	Genes in region	Ref
Vitamin B6	1p36.12	*ALPL, NBPF3*	[150]
Vitamin D (and insufficiency)	11p15.2	*CYP2R1*	[152–154]
	11q13.4	*NADSYN1,DHCR7*	
	4q13.3	*GC*	
Alpha-tocopherol, vitamin E response to vitamin E supplementation	11q23	*BUD13, ZNF259, APOA5, APOA4*	[137, 155, 156]
Vitamin E	12q24.31	*SCARB1*	[156]
	19p13.12	*CYP4F2*	
Dietary behaviors			
Habitual alcohol consumption	12q24.11-13	*CCDC63, MYL2, ALDH2, BRAP, CUX2,*	[157–160]
	7q11.22	*AUTS2*	
Habitual caffeine consumption, habitual coffee consumption	7p21	*AHR*	[20, 161, 162]
	15q24.1	*LMAN1L, EDC3, CYP1A2, CYP1A1, CSK*	
Habitual protein consumption	19q13.33	*FGF21, FUT1, FUT2, IZUMO1, RASIP1*	[163]

[1] Data were obtained by queries of the NHGRI catalogue of GWAS [164] (www.genome.gov/gwastudies, accessed June 2013) with additional data reported in supplementary material published by Kettunen et al. [135]. For the latter, we restricted tabulations to SNP-metabolite associations although several SNP-metabolite ratios also were identified

[2] For most traits multiple significant SNPs have been identified at each locus. Interested readers should review the study reference provided for a list of SNPs and study-level details

(SNPs) have been associated with variation in plasma levels of iron and omega-3 fatty acids and consumption of dietary protein, alcohol, and coffee, all of which are dietary factors implicated in T2D [8–13]. Knowledge of the genetic determinants of diet response or behavior may provide insight into underlying mechanisms and ways to study the potential health effects of diet more comprehensively by using genetic determinants as instrumental variables or by taking into consideration gene-diet interactions. Other products of the GWAS era, besides the newly identified variants, such as consortium and innovative statistical design, have greatly advanced the way such investigations are currently being conducted. Recent work aiming to confirm or refute causal effects and/or gene-environment interactions has involved cohort collections that are far larger than those utilized in the pre-GWAS era; this work has been facilitated by advanced meta-analysis techniques to combine data, and/or the availability of extensive replication materials [14, 15•, 16, 17]. The majority of published GWAS have reported on disease-associated loci, but more recently GWAS has been extended to examine variation in nutrient-response or behavior. Adverse effects of several established T2D-associated loci may be attenuated by adopting healthy lifestyle behaviors, such as high physical activity, whereas low physical activity and a Western dietary pattern have been found to augment genetic risk [15•]. In a recent study among three independent cohorts of adults predisposed to obesity by virtue of a high genetic score of established obesity risk loci, the genetic effects were significantly more pronounced in those who consumed high quantities of sugar-sweetened beverages compared with those who did not [18••].

The currently known susceptibility loci for T2D explain only 5-10 % of the previously estimated heritability of the disease [6••] and add only modestly to traditional disease risk factors in prediction models [19•]. Likewise, SNPs associated with dietary behaviors explain very little of the trait variance and/or heritability [20]. This partly reflects the complexity of behaviors and metabolic disease, which is further compounded by measurement error ascribed to their assessment within- and between populations [21]. Knowledge gleaned by other system-level data may greatly facilitate continued progress in these areas of human genomics.

System Level II: Human Transcriptome

The transcriptome is the complete set of messenger RNA molecules in a cell or a tissue at a given time. Unlike the genome, which changes very little during a person's lifetime, the transcriptome (as well as the proteome and metabolome) can vary by developmental stage and environment [22]. Because transcript quantification requires sufficient volumes of high-quality homogenous cellular material, human studies often are restricted to biopsies from accessible tissues, such as subcutaneous adipose tissue, skeletal muscle, and peripheral blood mononuclear cells [23]. Blood is the most feasibly collected in a population setting, but its use in gene expression

assumes that it provides *general* information on transcription in different cells and tissues, including those more relevant for the phenotype or disease of interest. GW expression studies of T2D have been predominately small, cross-sectional by design, and without replication [24]. Only recently has the approach been applied to incident T2D: a GW screen of miRNAs in the Bruneck cohort revealed a plasma miRNA signature for incident T2D that includes loss of endothelial miR-126 [25]. The latter plays a pivotal role in maintaining endothelial homeostasis and vascular integrity [26].

Numerous human intervention studies have used transcriptomics to characterize molecular response to dietary factors such as dietary fatty acids [27–31], carbohydrates [32], probiotics [33], folic acid [34], olive oil [27, 35], creatine monohydrate [36], vitamin E and selenium [37], CoQ10 [38], soy isoflavones [39], and different diets [40–44]. Most reveal significant yet subtle changes in transcript levels. Convincing human evidence suggests that many of the biological effects of unsaturated fatty acids are mediated through modulation of gene transcription by regulating the activity of transcription factors, such as peroxisome proliferator-activated receptors, retinoid X receptor, liver X receptor, and sterol regulatory binding proteins [23]. In light of emerging data showing gut flora compositions (or "microbiota") differ between healthy individuals and diabetics or obese [45–47], results from gene expression measures of duodenal mucosa following supplementation of Lactobacillus GG are encouraging. Lactobacillus GG, also found in yogurt and other fermented foods, altered the expression of genes involved in immune response and inflammation, apoptosis, cell growth and cell differentiation, cell–cell signaling, cell adhesion, and signal transcription, and transduction [33].

Altered transcript levels in response to diet can inform mechanisms of action but whether such changes observed in nutritional intervention studies have relevance to a population setting and/or are large enough to have any impact on disease development is an open question. Little is known about whether or how specific dietary factors induce changes in gene expression of disease target tissue. To acquire such knowledge our only feasible option might be to complement human data with that obtained from experimental models. Genome-wide expression profiles collected from mouse liver and adipose tissue are notably enriched for altered transcripts of immunity-related genes when their high fat diets are supplemented with coffee [48]. Coffee suppressed expression of liver cytokine interleukin (IL)-1β and MCP-1 gene expression in white adipose tissue [48]. Given the role inflammation may have in development of T2D [49], these observations suggest a relevant mechanism by which coffee might reduces risk of the disease in humans. Nearly all GW scale studies concerning diet-induced changes in gene expression of pancreatic β-cells, a key target tissue for T2D, originate from rodent animal models or cultured cell lines [50•]. While offering insight to tissue-specific gene-expression not easily obtained from humans, experimental studies are not without limitations and will warrant caution when translating to humans.

System Level III: Human Proteome

Transcript levels do not always correspond to protein levels, stressing the need to study proteins directly. The proteome may contain over a million structurally different proteins performing distinct functions in an individual and the goal of proteomics is to simultaneously quantify these proteins in biological samples [51, 52]. Currently, no single analytical platform is able to capture the full spectrum of proteins; those present at low concentrations and abundance are especially difficult to detect and characterize [53]. Metabolic diseases, such as diabetes, involve various affected tissue and because all are in contact with blood, tissue-specific proteins with diagnostic potential might be recovered in the circulation [52]. Blood is therefore an attractive biospecimen for protein profiling in population settings but also is the most complex to study [52]. Many individual serum proteins, such as interleukin-6, resistan, leptin, and adiponectin, have been shown to vary between healthy and insulin-resistant (IR) or diabetic individuals [54–57], lending some support to the potential for global protein profiling. Indeed, the few small-scale studies that have applied proteomics have revealed potentially novel biomarkers of IR or T2D [58]. These include blood circulating flotillin-1, arginase, syntaxin 1C, haptoglobin, and complement C3 [59, 60]; mitochondrial, cytoskeletal, proteasome, and chaperone proteins in skeletal muscle [61]; and structural and stress/unfolded protein response proteins in subcutaneous adipose tissue [62]. Proteomics applied to human nutritional intervention studies have ranged from 1 to 12 weeks in duration and have, for example, tested soy isoflavones [63], flaxseed [64], fish oil [65], folic acid [66], and anti-inflammatory mixtures [67]. Serum levels of inflammatory and lipid proteins, such as APOA1, zinc-a-2-glycoprotein, haptoglobin precursor, amyloid P component, and hemopexin, are down-regulated by 6 weeks of fish oil compared with sunflower oil supplementation [65]. Following 8 weeks of 25 mg of isoflavone supplementation, blood cell levels of proteins promoting fibrinolysis (i.e., alpha-enolase) were higher, whereas those mediating adhesion, migration, and proliferation of vascular smooth muscle cells (i.e., galectin-1) were lower [63].

Thus far, proteomics has had limited application to population studies of human metabolic disease or nutrition. To our knowledge, no prospective proteomic studies of T2D have been conducted, and the few population-based studies of nutritional factors have been small and have all targeted <60 proteins [68–71], most of which are from the inflammatory and/or oxidative stress classes of proteins. However, with continued advancements in the field, such as high-throughput tools for the fractionation of biological samples and growing

databases housing tissue-specific protein reference maps, this pattern promises to change in the near future.

Systems Level IV: Human Metabolome

Metabolomics involves the comprehensive analysis of all measurable metabolite concentrations under a given set of conditions [72, 73]. These metabolites are the final products of preceding "omic" processes and their interaction with intrinsic and extrinsic factors [72, 73]. Thus far, more than 37,000 unique metabolites have been identified in human specimens [74, 75] (http://www.hmdb.ca, accessed June 2013). Similar to the proteome, no single analytical platform captures the full spectrum of metabolites. Analyses can be conducted in an untargeted manner, typically optimized for broad coverage of the metabolome to enhance opportunities of discovering discriminatory features of a disease/trait, or in a targeted manner, profiling only a defined set of known metabolites to enable improved sensitivity and efficiency [76]. Metabolomics is increasingly applied in the clinical and population setting. Detailed technological and conceptual challenges as well as progress in the broader field have been discussed elsewhere [77•].

Recent metabolomic studies of T2D have considerably improved upon the earlier cross-sectional reports [78, 79]. Among adult population-based studies involving up to 800 incident cases, targeted metabolite profiling has identified an array of novel metabolite classes linked to T2D onset, such as short- and medium-chain acylcarnitines, the specific lipid classes of sphingomyelins (SMs), lysophosphatidylcholines, phosphatidylcholines (PCs), and lysophosphatidylethanolamines, and branched-chain amino acids (BCAAs) [80, 81, 82••, 83, 84]. Some of these classes also have been linked to obesity and other T2D-related traits [85–90]. Patterns linked with T2D among adults have not always been replicated in younger populations [91, 92], supporting the need for longitudinal monitoring to enable trajectory analysis of metabolic responses. Further work is needed to determine whether these metabolites are elevated because of an individual's genetic or diet characteristics, and/or the actions of gut microbes [93]. Interestingly, high dietary protein intake is associated with T2D and higher plasma levels of BCAAs [8, 94]. PCs occur in animal and plant tissues and are therefore present in the diet (e.g., eggs and soy beans). Recent work suggests these phospholipids are further metabolized by intestinal microbiota, producing the proatherosclerotic metabolite trimethylamine-N-oxide [95, 96••, 97, 98].

Metabolomics has been used to characterize the complex human metabolic effects of specific foods, nutrients, and dietary patterns in both the clinical and population setting [99, 100, 101•, 102–107]. Intervention studies of coffee [108–111], tea [112, 113], cocoa [114, 115], nuts [116], dietary fiber [117], vitamins and selected nutraceuticals [67, 118], for example, have incorporated either targeted or untargeted metabolite profiling. Earlier reports have favored the presentation of exogenously derived metabolites. Confirmed metabolite markers of coffee exposure, for example, include mainly methylxanthines and reduced, sulfated, and methylated forms of hydroxycinnamates [108–111], which are coffee-derived metabolites. There is, however, an increasing interest in the impact foods have on the endogenous metabolome (known as the "host response") [115]. Potential markers of nut intake include conjugated fatty acids, serotonin metabolites, and microbial-derived phenolic metabolites [116]. Metabolites linked with carnitine metabolism, sulfation of tyrosine, and gut microbial metabolism are among the set of metabolites linked to cocoa intake [115]. Evidence for diet-induced altered intestinal microbiota metabolism is particularly relevant in light of results from metabolomic studies of T2D and other system-level results discussed above.

Population-based studies designed to identify metabolite signatures of self-reported dietary intake have targeted a similar set of metabolites to that of recent metabolomic studies of T2D (i.e., lipids, amino acids and their derivatives). In a population sample of men, coffee intake was positively associated with specific classes of SMs and negatively associated with long- and medium-chain acylcarnitines in plasma [119], classes previously linked to reduced and increased risk of T2D, respectively [80, 81, 120–122]. The negative association between coffee and medium-chain acylcarnitines was later confirmed in an independent study of women from the TwinsUK cohort [123], which additionally identified metabolites associated with garlic, fruit, and vegetable intake and hypocaloric dieting [123]. Of relevance to the utility and interpretation of metabolomic approaches applied to populations is recent work by Heinzmann et al. [124•] and Krug et al. [101•], showing that interindividual metabolic differences influence proportionally more of the spectrum of metabolites than dietary modulation, although certain individuals display a greater stability of metabolic phenotypes than others [101•, 124•]. Some of this stability is likely heritable; in the TwinsUK study mentioned above, two thirds of the metabolites associated with nutritional patterns had a significant genetic contribution, and the remaining third were solely environmentally determined [123].

Metabolomics has already provided new insight to chronic disease development and response to diet. Its application in a population setting might further enable epidemiologists to separate metabolites resulting from inherited patterns of metabolism from those that are entirely due to environment [123]. This particular task will greatly benefit from findings of other system-level analysis, the most apparent being genomics. Indeed, several GW-confirmed loci are associated with variation in plasma levels of metabolites implicated in T2D and additionally influenced by diet (Table 1) [125]. Recent metabolomic successes have been based on only a fraction or two of the full spectrum of metabolites. Ongoing efforts to

characterize the existing "unknowns" will soon enable more exhaustive investigations.

Future Directions: Human Systems Integration

As outlined above, each system level has potential to reveal insight to disease development and response to diet. Besides single SNP-, transcript-, protein-, and metabolite-trait testing, network analysis (knowledge-driven) or computational modeling of all system-level data-points (data-driven) also may be performed. Integrating system-level data from external resources is another feasible and highly efficient approach epidemiologists are taking to maximize "omic" data [126–128]. However, extrapolating results from an integrative analysis of potentially diverse datasets does not provide a complete understanding of the human system and its responses to diet as a whole. Intermediate molecular quantitative trait locus (iQTLs) analysis has been one advancement towards integrating large-scale omic data [22, 129]. In iQTL mapping, transcripts, proteins, metabolites, or other heritable physiological factors serve as traits for genetic association analysis, the rationale being that these intermediates (or endophenotypes) more closely underlie genetic risk than heterogeneous behavioral or disease phenotypes [129, 130].

The *ideal* system-wide study would have multi-omic data for an individual collected at multiple time points along with exposure details and longitudinal follow-up. Chen et al. [131••] recently explored this concept of an "integrative personal omics profile" (iPOP) by combining several omic-profiles from a single individual during a 14-month period. iPOP revealed various health risks, including T2D and uncovered extensive, dynamic changes in diverse molecular components, and biological pathways across healthy and diseased conditions. This iPOP framework might easily be upscaled to a nutritional intervention study. The most ambitious systems epidemiology approach would apply this iPOP framework to a population-setting. Harnessing the resources of existing large prospective studies of lifestyle and chronic diseases, which have archived biological samples and repeated measures of diet and lifestyle, would be the most efficient approach to reaching this goal [1]. This strategy was recently applied to a subset of individuals participating in the Finnish population-based Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM) study [132] and preliminary cross-sectional analysis are promising. Network analysis of transcriptomic and metabolomic data available from 518 individuals identified genes from the lipid–leukocyte (LL) module as having a key role in more than 80 metabolites, including lipoprotein subclasses, lipids, and amino acids. Genomic variation was used to infer this module's reactivity to fatty acids and high/low/intermediate-density lipoprotein fractions. Parallel associations with plasma IL-1 receptor antagonist, C-reactive protein, and adiponectin suggested the LL module as a possible link between inflammation, metabolism, and adiposity [132].

Although beyond the scope of the current paper, there are several important issues that still need to be resolved before considering system tools in the broader field of systems epidemiology. For example, a common goal in epidemiology is to relate a "usual" level of an exposure with the risk of disease [133] and an outstanding concern pertains to the fact that transcript, protein, and metabolite levels vary with time and recent environmental factors. Quantifying and identifying the source of this variation and the extent to which this variation impacts power for detecting associations warrants further study [134•]. How repeated measures may remedy this concern also is an open question. Another issue is that the multiple-testing problem is likely to be magnified in multi-omic studies, which will have significant impact on the power and data interpretation. Epidemiologists will need to be mindful of these and other limitations when designing and interpreting system-wide studies.

Conclusions

Nutritional systems epidemiology has potential to provide new insight into underlying mechanisms and ways to study the health effects of specific foods more comprehensively. Coincident with advancing nutrition research, it has incredible potential to finally realize the *concept* of personalized nutrition. Continued technological advances in sensitive high-throughput methods, enhanced bioinformatics and analytical tools, and reduced costs will enable more widespread use of these techniques in nutrition and epidemiological research. However, critical to the success of this approach is well-designed prospective cohort studies with very large size, long-term follow-up, high rates of follow-up, availability of archived biological samples, and detailed measures of diet and lifestyle. Our brief summary of selected studies across systems already yield impressive results and when merged with equivalent applications to T2D provide compelling evidence that the goal of personalized *optimal* nutrition for prevention and treatment of disease will become increasingly attainable by systems epidemiological approaches.

Compliance with Ethics Guidelines

Conflict of Interest Marilyn C. Cornelis declares that she has no conflict of interest relevant to this review.

Frank B. Hu declares that he has no conflict of interest relevant to this review.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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