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From Neighborhood to Genome: Three Decades of Nutrition-related Research from the ARIC Study

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Abstract

For 30 years, the Atherosclerosis Risk in Communities (ARIC) cohort study has examined the etiology and progression of atherosclerosis and atherosclerotic diseases.[1] This research has evaluated variation in cardiovascular disease (CVD) risk in relation to age, race, gender, location and lifestyle factors, including diet. In this commentary, we describe ARIC research that illustrates an expanded view of the relationship between diet and health and suggest ways that future cohort studies may influence the direction of nutrition and dietetics practice.

Keywords

cohort studies; nutrigenomics; dietary quality indices; geographical information systems; epigenetics

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Conflict of Interest Document
No authors report a conflict of interest.

ARIC Background

In the early 20th century, food policy and dietary guidance focused on prevention of foodborne illnesses and nutritional deficiencies. Later in the century, the prevention and control of chronic disease became priorities.[2,3] The nutrition and dietetics professions have evolved in response to increasing knowledge of chronic disease risk factors, new treatments and lifestyle strategies for prevention,[4] rising rates of obesity and obesity-related chronic diseases, and persisting racial and ethnic health disparities in heart disease, hypertension and diabetes.[5–7] Beginning with the Framingham Heart Study in 1949, multi-center cohort prospective observational studies have examined the relationships between chronic disease and diet.[8] Starting in 1987 and sponsored by the National Institute of Health's (NIH) Heart, Lung and Blood Institute, ARIC has been studying a cohort of individuals born before or during WWII through four field centers (Wake Forest Baptist Medical Center [Forsyth County, NC], University of Mississippi [Jackson, MS], University of Minnesota [Minneapolis suburbs], and John Hopkins University [Washington County, MD]), a coordinating center (the University of North Carolina) and numerous collaborating centers.[1] From 1987–1989, a sample of 15,792 whites and African Americans aged 45–64 years was recruited. Using probability sampling, each ARIC field center recruited approximately 4,000 individuals aged 45–64 from a defined population in their community.[9] Only African Americans were recruited in Jackson; remaining sites reflected local populations, mostly white in Minneapolis and Washington Co. and both races in Forsyth Co. The Institutional Review Boards from all centers approved ARIC protocols including compliance with NIH protocols for the protection of genetic information. Participants provided written consent for their study participation and for use of their genetic data. To date there have been six exams, baseline/visit 1 (1987–1989), visit 2 (1990–1992), visit 3 (1993–1995), visit 4 (1996–1998), visit 5 (2011–2013) and visit 6 (2016–2017) with telephone follow-up conducted annually between visits. Examinations occurred at a local research clinic; if necessary, a shorter examination at the clinic or at participant's home or care facility are substituted. Participants were compensated for their time and travel. As of 2016, the cohort is comprised of approximately 9000 participants. ARIC funding continues through 2021 and new investigators are invited to become involved in the study.[10]

Assessments include, but are not limited to, medical history, anthropometrics, blood pressure, glucose, biochemical measures, pulmonary function, carotid artery ultrasound measures, genotyping and behaviors (smoking, diet and physical activity). Investigators have received additional funding for ancillary studies that have supported magnetic resonance imaging (MRI) of the brain, cognitive and physical function, among other topics.

Dietary data were obtained with the interviewer-administered ARIC 66-item modified Harvard food frequency questionnaire (FFQ) at Visits 1 and 3.[11] From the FFQ, dietary intake was calculated using the Harvard Nutrient Database.[12] The original validated 61-item Harvard FFQ developed primarily among white women was modified by ARIC to include four fish categories, pasta, cake and bread items, and a single sugar-sweetened soft drink category; alcohol items were removed and queried separately. The reliability of the ARIC FFQ was assessed using dietary data from the baseline/visit 1 (1987–1989) obtained from all participants and from an additional dietary assessment obtained in visit 2 (1990–1992) from a subset of 443 subjects randomly selected from all sites.[13] Mean time elapsed between these exams was three years. Reliability coefficients were higher among men, whites, individuals with >12 years of education and those between 45–49 years old.

ARIC published 117 nutrition-related articles from 1992 through August 2016. For this commentary, the first author constructed a database documenting each report's aims, dietary or nutrition-related measures, participant characterization, biochemical and metabolic assessments, health outcomes, statistical analysis and key findings (Microsoft Access, Microsoft Office Professional 2010, version 14.0.7015.1000). A review by all authors of the methods found in the database found that most articles evaluated single foods or nutrients in relation to advanced biochemical and metabolic assessments, chronic disease and mortality outcomes, and demographics (age, gender, race and education). Studies investigated micronutrients (phosphorus, magnesium, iron, potassium, zinc, choline and betaine, vitamins A, C, D, and E and B vitamins), macronutrients with an emphasis on dietary fats (cholesterol, and saturated [SFA], monounsaturated fats, types of polyunsaturated fats [PUFA]), and individual foods (fruits, vegetables, dairy, fish, eggs, red and processed meats, poultry, whole and refined grains, salty snacks, nuts, sweets, soft drinks, alcohol and coffee).[14–23] Details of these reports are found in the Supplemental Table. However, there were three investigative approaches that expanded ARIC's nutrition-related methods; these were dietary pattern analysis, neighborhood effects on diet and health, and nutritional genomics techniques. This commentary provides an overview of these three methodological approaches using 27 ARIC reports to illustrate the methodologies. Details of these 27 reports are also found in the Supplemental Table.

Dietary Pattern Analysis

Beginning with 19th century research about vitamin structure and function, investigations of individual nutrients became critical to understanding metabolic pathways and biomarkers of disease.[2,24] However, many nutrients and foods influence similar pathways making it difficult to separate the multiple small health effects of a single nutrient or food from the rest of the diet.[24–26] As early as 1950, researchers identified the effects of food patterns on health, such as the diets of Mediterranean countries on CVD risk.[27] Today supported by evidence from nutrition epidemiology and lifestyle and clinical interventions, research on the cumulative and synergistic effects of dietary patterns has expanded using both *a posteriori* and *a priori* methods.[28–30]

A posteriori or "data driven" methods use existing datasets and multivariate analysis to identify dietary patterns within a sample and relate these patterns to characteristics of that same sample.[31] With 10,000 participants from all sites, Lutsey et al. examined the relationship between dietary patterns and onset of metabolic syndrome (MetS) up to nine years after baseline.[32] Dietary patterns as measured by ARIC's 66-item FFQ were based on the average of dietary intakes from visit 1 (1987–1989) and visit 3 (1993–1995). Similarly, Steffen et al related dietary patterns of 15,000 ARIC participants to the development of venous thromboembolism (VTE) over a 12 year period.[21] In a third study, diet was assessed in 2005–2006 among 1000 white participants using the Willett 131-item FFQ and dietary patterns were related to cell activation and inflammation markers.[33] The principal components analyses from these three studies identified similar dietary patterns.[21,32,33] "Western" patterns were characterized by high intakes of refined grains, processed meat, fried foods, red meat, refined grain desserts, sweetened beverages, and cheese and whole milk. "Prudent" or "Healthier" patterns reflected higher consumption of vegetables, fruit, fish, poultry, and whole grains. MetS and VTE were positively associated with Western pattern and five cell activation and inflammation markers were positively associated with Western pattern and inversely with the Healthier pattern. Although studies differed in sample size, racial composition and participants' age at the time when diets were assessed, these results demonstrate generalizability of "healthy" and "unhealthy" dietary patterns and suggest stability of these patterns over time.

A priori composite measures utilize results from prior epidemiological or clinical research to create standardized tools for dietary assessment, such as dietary quality indices.[30] These indices provide component scores representing food categories relevant to health and a total score representing overall dietary quality.[34] Indices, such as Healthy Eating Indices (HEI),[35,36] Dietary Approaches to Stop Hypertension (DASH) Index[37], and Mediterranean Diet Index,[38,39] share food groups including fruits and vegetables, whole grains, nuts, legumes, unsaturated fats, red meat, processed foods, sodium and sugar-sweetened beverages. ARIC's Healthy Food Score (HFS) identified similar dietary components based on evidence from prior research about the relationship between diet and blood pressure (BP).[40] Hypertension was inversely associated with HFS total score and its dairy and nut components, and positively associated with the meat component.[40] In 2010, the American Heart Association defined the concept of cardiovascular health using ideal health behaviors (nonsmoking, body mass index [BMI] <25 kg/m^2 and adherence to current dietary and physical activity guidelines) and ideal health factors (untreated total cholesterol <200 mg/dL, untreated BP <120/<80 mm Hg, and fasting blood glucose <100 mg/dL).[41] To monitor these factors over time, the organization developed metrics known as Life's Simple 7. Metrics included three health behaviors (diet, exercise and smoking) and four health factors (cholesterol, BMI, BP, and fasting blood glucose). Diet is assessed with the Healthy Diet Score (HDS), which contains recommended intakes of fruit and vegetables, fish, fiber-rich foods, sweetened beverages, and sodium. ARIC has shown that African Americans have the lowest rate of compliance for HDS and other Simple 7 measures.[42] However, African Americans with high rates of Simple 7 compliance have comparable CVD risk as whites with similar compliance rates.[42]

Future Applications

In future cohort studies, both dietary pattern analysis and quality indices should be assessed at each time point. Dietary pattern analysis provides a way to identify subgroups with common food habits and to monitor changes in their dietary patterns and biomarkers over time. Standardized dietary quality indices can help monitor how well the diets of cohorts are meeting current recommendations and to compare their diets to those of other cohort samples or national population-based samples, such as NHANES, the on-going National Health and Nutrition Exam Survey.[43]

Neighborhood Effects on Diet and Health

Where an individual lives is probably the most comprehensive single measure of SES and community conditions.[44,45] In 1990, ARIC began assessing the relationship between neighborhood and health utilizing geographic information systems (GIS).[46–52] Census blocks and tracts were linked to participants' 1990 addresses; these defined areas served as proxies for neighborhood. Neighborhoods were linked to socio-demographic information from the 1990 Census and survey data of the locations of food stores and food service outlets.[46–48] Nine years after baseline, compared to affluent individuals living in the most advantaged neighborhoods, whites or African Americans who were poor and lived in disadvantaged neighborhoods had overall and CVD mortality risks equivalent to being more than 10 years older at baseline.[49] Wealthier and white neighborhoods had 3–4 times more large chain supermarkets compared to neighborhoods where low income individuals or African Americans lived.[50] When supermarkets were available, the effect for African Americans was more pronounced than among whites.[52] Fruit and vegetable requirements (at least 2 fruit and 3 vegetable servings daily) were 30% more likely to be met among African Americans living in neighborhoods with one supermarket and 200% more likely if there were two or more; when supermarkets were present, whites were only 11% more likely to meet requirements.[52] Finally, residents of neighborhoods with supermarkets were less likely to be obese or overweight and those living where convenience stores were prevalent were more likely to be obese or overweight.[51]

Future Applications

Geographic location can serve as a proxy for a range of neighborhood variables related to health and diet and therefore, geographic diversity within communities should be incorporated into recruitment strategies for future cohort and intervention studies.[53] Future geographic analyses of cohorts should consider location as a dynamic variable altered overtime by neighborhood changes and participant relocations and a variable which may be better understood if assessed at multiple time points.[54]

Nutritional Genomics

Nutritional genomics is a broad area of research that contributes knowledge about the interaction between nutrition and genes[55] and includes the fields of nutrigenetics, nutrigenomics, and nutritional epigenetics.[55–57] Nutrigenetics evaluates the influence of genetic variation on nutrient metabolism.[58] Nutrigenomics focuses on the effects of particular nutrients or foods on gene expression, thereby potentially altering gene function.[59] Nutritional epigenetics considers genetic variation as on-going process in which exposure to certain nutrients or food components have potential to modify the function of genes.[60] ARIC has evaluated nutrition-related genetic variation using all three of these approaches.

In an example of nutrigenetics, ARIC used a gene variant of the vitamin D binding protein (DBP) to evaluate the relationship between 25(OH)D and CVD risk as well as racial differences in vitamin D metabolism.[61] High levels of DBP are associated with lower amounts of bioavailable vitamin D.[62] Genetic variation in DBP can be related to the paradox that in general African Americans have lower levels of serum 25(OH)D compared to whites but comparable amounts of 1,25(OH)2D, a bioavailable form.[63] Researchers evaluated relationships among heart failure (HF), race, serum vitamin D (25(OH)D) and a gene variant of DBP.[62] Results showed that low serum 25(OH)D was independently associated with HF among whites but not African Americans and that regardless of race, those with genetic variant associated with high DBP had low 25(OH)D, which was associated with HF risk. ARIC research and similar reports illustrate how nutrigenetics can inform the development of race-specific dietary recommendations and disease-prevention strategies for specific populations.[64]

ARIC nutrigenomics research has utilized today's DNA scanning technology, which can reliably genotype up to a million single nucleotide polymorphism or SNPs (the substitution of one amino acid in a pair or a single genetic variant) from a single scan of an individual's DNA.[65] SNPs that are associated with particular disease risk in genome-wide association studies (GWAS) are further tested in larger or more racially or ethnically diverse samples.[65] The interactions between 17 SNPs of diabetes risk and the glucose lowering effects of whole grain foods were tested using data from 14 cohort studies, including the ARIC cohort, which represented 48,000 individuals of European descent without diabetes.[66] Specifically, the 17 SNPs were associated with higher fasting glucose and/or insulin concentrations. However, the ability to isolate an interaction between a single food and one gene variant is a tremendous challenge. Even with a large sample, replication in multiple cohorts and confirmation of glucose-lowering properties of whole grain foods, the single nominally significant interaction between whole grain intake and one SNP disappeared after the required adjustment for multiple statistical comparisons. In studies of total (dietary and supplemental) zinc and dietary magnesium, similar results were found.[67,68] Zinc and magnesium intake were inversely related to blood glucose and for each nutrient, only a single nominal or unadjusted significant interaction between numerous gene variants associated with glycemic control was identified. To address the challenges of single SNP comparisons, ARIC has used genetic risk scores (GRS), which are genome-wide composite scores comprised of multiple SNPS identified through GWAS.[69] GRS aggregate genetic information, reduce measurement error, and consider cumulative effect of many small risks.[70] ARIC evaluated separate GRS for low-density lipoprotein, high-density lipoprotein, triglycerides and total cholesterol in relation to abnormal lipids and incident usage of lipid-lowering medications among 10,000 white participants from multiple cohort studies.[71] Lipid GRS were positively associated with abnormal lipid levels and greater use of lipid medication at baseline but these GRS were not associated with the rate of change in these measures over the following nine years. Future GWAS among more diverse cohorts and those consuming more varied diets are needed to better understand how diet and genetic variation contribute to health risk, particularly among non-European populations.[70] These studies can help develop personalized diet therapy based on GRS and explain high rates of obesity and diet-related chronic disease found among racial and ethnic groups who have adopted the meat and refined grain diets of Western countries.[72]

Epigenetics considers genetic variation as a dynamic process in which environment and lifestyle have potential to modify the function of genes.[73] These heritable changes do not alter DNA sequence but can alter gene expression and cell function.[73] DNA methylation is one of several mechanisms that affect DNA structure and function and is the one studied most extensively. DNA methylation occurs when a methyl group is added to the cytosine of a gene's DNA altering its structure and potentially modifying its function.[74] Epigenetic-wide association studies (EWAS) are used to identify methylation patterns across DNA regions. For example, adipose tissue is a prime epigenetic target because of its known effects on inflammation and oxidative stress that can lead to DNA methylation and other epigenetic changes.[75–77] Excess adipose tissue, represented by BMI and/or waist circumference, was associated with 300 DNA methylation sites identified in EWAS conducted among 2,000 African Americans in ARIC.[78] These methylation sites were associated with carbohydrate, lipid and energy metabolism pathways and provide focus for future research about mechanisms by which dietary intake influences epigenetic alterations or can mitigate or intensify its effects.[73,78,79]

Future Applications

Nutrition genomics research is growing in complexity and scope.[56] In the future, race-specific dietary guidelines and clinical recommendations may emerge; new cohort studies will identify specific foods that could have health benefits for the general population; and diets tailored for specific genomic profiles may be marketed to the general public.[80] As a result, nutrition and dietetics professionals need timely and relevant information about these advances and research to learn how to successfully communicate complex genetic concepts to lay audiences and patients.

Conclusion

ARIC nutrition research reflects our contemporary understanding of the multi-dimensional nature of food and the wide range of human diversity represented by genes, environment, culture and many other factors. Future prospective cohort studies that integrate genomic profiling, geographic analysis and dietary pattern assessment will help tailor dietary guidance to the needs of those predisposed to chronic disease and influence the ways in which communities can improve the health of their most vulnerable populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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