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Challenges of the heterogeneous nutrition response: interpreting the group mean

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Extensive research demonstrates unequivocally that nutrition plays a fundamental role in maintaining health and preventing disease. In parallel nutrition research provides evidence that the risks and benefits of diet and lifestyle choices do not affect people equally, as people are inherently variable in their responses to nutrition and associated interventions to maintain health and prevent disease. To simplify the inherent complexity of human subjects and their nutrition, with the aim of managing expectations for dietary guidance required to ensure healthy populations and individuals, nutrition researchers often seek to group individuals based on commonly used criteria. This strategy relies on demonstrating meaningful conclusions based on comparison of group mean responses of assigned groups. Such studies are often confounded by the heterogeneous nutrition response. Commonly used criteria applied in grouping study populations and individuals to identify mechanisms and determinants of responses to nutrition often contribute to the problem of interpreting the results of group comparisons. Challenges of interpreting the group mean using diverse populations will be discussed with respect to studies in human subjects, *in vivo* and *in vitro* model systems. Future advances in nutrition research to tackle inter-individual variation require a coordinated approach from funders, learned societies, nutrition scientists, publishers and reviewers of the scientific literature. This will be essential to develop and implement improved study design, data recording, analysis and reporting to facilitate more insightful interpretation of the group mean with respect to population diversity and the heterogeneous nutrition response.

Inter-individual variation: Personalised nutrition: Population diversity: Race/ethnicity: Sex as a biological variable

Extensive research has demonstrated unequivocally that nutrition plays a fundamental role in maintaining health and preventing disease[1]. In parallel, nutrition research provides evidence that risks and benefits of diet and lifestyle choices do not affect people equally, as people are inherently variable in their responses to nutrition and associated interventions to improve or maintain health[2–10]. Difficulties in generating unequivocal evidence is costly in terms of wasted research effort, causes confusion[11] and biased reporting[12–15]. Hence, nutrition research faces significant challenges in determining responses to diet and lifestyle interventions to improve and maintain metabolic health and prevent diet- and lifestyle-related diseases. In efforts to address these challenges, nutrition science has striven to simplify the inherent complexity of human diets and lifestyle factors, with the aim of managing expectations for dietary guidance required to ensure healthy populations. This has necessitated development of approaches in nutrition research that seek to group individuals based on various criteria to determine mean responses to diet and nutrition interventions to improve health and prevent diet- and lifestyle-related diseases by comparing the mean responses of assigned groups. Different measures of centre may be applied to response data from these studies, including mean, median and mode. However, such studies are often confounded by the heterogeneous nutrition response[2–4,8,9,16,17]. This presents difficulties in attempts

Abbreviations: NCD, non-communicable diseases; SABV, sex as a biological variable.

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to assign a representative 'typical' group response and summarise data with a single number. Increased prevalence of diet- and lifestyle-related non-communicable diseases (NCD) adds to the pressure on nutritional scientists to address the heterogeneous nutrition response[17–20].

Recent decades have witnessed the emergence of novel technologies and research fields that may permit the development of new approaches to tackle the heterogeneous nutrition response[16,21–27]. This has largely been prompted by the recognition of interindividual variation in disease risk and responses to interventions and the advances in tools and technological platforms, generally alluded to as omics technologies[28–30]. Adoption of omics technologies has spawned the emerging fields of personalised/precision nutrition and molecular epidemiology[31,32]. The search for solutions to the burden of NCD is driving the need for integration and application of omics technologies to characterise heterogeneous nutrition responses. This will require greater consideration of aspects of study design, data recording, analysis and reporting to facilitate more insightful interpretation of traditional approaches to interpreting the group mean and address human diversity. This has implications for all aspects of nutrition science.

This review paper will explore some of the commonly used criteria applied in grouping study populations and individuals that are then used to conduct comparisons, with the intention of identifying the mechanisms and determinants of responses to nutrition. Consideration of the challenges of interpreting the group mean in diverse populations will be reviewed with respect to both human studies and *in vivo* and *in vitro* model systems. The potential for improved study design, data recording, analysis and reporting to facilitate more insightful interpretation of the group mean will be explored with respect to population diversity in general and specifically, with a focus on diversity associated with race, ethnicity, sex and gender.

Population diversity and compiling groups

Compiling groups in nutrition research, in attempts to decrease the inherent complexity and diversity of human populations and their nutrition, present a dichotomy. Analysis is inevitably directed to comparing group means to interpret nutrition responses to generate meaningful conclusions from nutrition research. However, this often contributes to recording non-significant differences from group comparisons, despite clear evidence of responders and non-responders within study groups[2,3]. Alternatively, depending on the recruitment and composition of the group, contradicting and contrasting results can be recorded for similar nutritional interventions[4,8]. This contributes to considerable wasted research effort, biased or skewed reporting[12–15] and much confusion among the public and within the scientific community[11].

The awareness of links between diet and disease risk and the potential to identify effective nutritional interventions to prevent disease and maintain health, initiated attempts to group individuals based on various criteria. For example, common and extensively used criteria include chronological age, 'healthy' individuals, overweight/obese, race/ethnicity and male/female. There are many other factors which impact on population diversity and influence heterogeneous nutrition responses and warrant consideration. However, this limited list serves to illustrate the potential for failure to recruit homogenous groups to facilitate the generation of meaningful conclusions based on analysis and reporting of the group means. These common and extensively applied criteria for compiling groups for nutritional research highlight various pitfalls, which are further considered below.

Chronological age is often a poor indicator of biological age[26,33,34], which can have a profound impact on nutritional responses. 'Healthy' individuals are recruited without underlying health issues or pertinent history being assessed in detail. BMI is often used as a surrogate to recruit and assign groups with respect to normal, overweight or obese, despite BMI being an imprecise measure of obesity[35]. Individuals with obesity or diabetes present a large proportion of populations[36,37]. However, study of groups recruited on obesity or diabetic status do not provide homogenous groups. There is a broad range of differing metabolic health and biological responses that contribute to diversity in individuals with obesity[38] and diabetes[39].

Population diversity can change over time due to changes in behaviour leading to altered disease prevalence, pathophysiology and introduction of prescribed medications. Many individuals using prescribed medications will subsequently be excluded from nutrition research, despite such medications being used by substantial proportions of human populations. Many commonly used medications can alter nutritional requirements and responses. For example, hormonal contraceptives are widely used by females throughout the world[40]. Biological sex, a known lipidomic factor, is enhanced by hormonal contraceptives[41]. Lipidomics has emerged as a target for biomarker discovery and assessment of nutritional responses[42,43]. However, nutrition research often excludes women and if recruited to nutrition studies women taking hormonal contraceptives are often excluded. The use of statins to lower plasma lipids has increased rapidly since their introduction in the 1990s[44]. However, research on dietary guidelines for dietary fats are lacking in this group, since statin use is often an exclusion factor in compiling groups in which lipids will be used to assess nutritional responses. The following sections will further explore specific challenges of addressing population diversity and compiling groups based on race, ethnicity, sex and gender.

Race, ethnicity and genetic diversity

Genetics plays a role in inter-individual variation, prompting studies to compile groups by assigning race and ethnicity to explain observed differences in NCD linked to common genetic ancestry[45,46]. However, the scientific basis for determining ethnicity is often vague

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and the evidence for race is weak[47,48]. Methodological concerns with standard approaches to measuring race and ethnicity determined that they often failed to adequately differentiate either. This supported advocates of more inclusive response options[49] and was a starting point for improved race and ethnicity recording and data analysis. However, reports that race and ethnicity responses may change over time and context indicated that the solution to improving race and ethnicity was not a simple one[50]. Liebler *et al.*[50] reported that about 9·8 million (6·1 %) individuals reassigned their race between US Census Bureau data collected 2000 to 2010 from 162 million responses linked at the individual level. This confounds downstream analyses and interpretation of results from groups assigned to different racial or ethnic groups. This also has implications for the compilation of research evidence presented on race/ethnicity in reviews, including systematic reviews.

Evidence of detrimental impacts on health care and research in different racial and ethnic groups, due to incomplete race and ethnicity data, prompted action from various quarters. The Department of Health in the UK produced practical guides to ethnic monitoring, which provided examples of good practice[51]. NHS Scotland introduced an ethnic monitoring tool[52]. However, concerns remained with regard to inaccurate, incomplete and unvalidated data collection relating to race and ethnicity[45]. This prompts the question: How good is race and ethnicity coding applied in nutrition research? This is an important consideration for study design. Without reliable race and ethnicity data, investigation and reporting of diet- and lifestyle-related diseases are compromised in these groups[45,53].

In addressing this issue, genetic diversity must be carefully considered. Following sequencing of the human genome researchers have intensively studied genetic diversity and identified genetic admixtures in the human population that are spread throughout the globe[54]. Data from genome-wide association studies is now being interrogated to generate fine-scale genetic differentiation in populations throughout the world[55–59].

This has revealed detailed genetic analysis of populations in Britain, dispelling the perception of a general Celtic or Anglo-Saxon population[57]. While studies of genetic structure of individuals in Western France provide evidence of rare and geographically localised genotypes with links to Irish populations and other European populations, including the Netherlands, Britain and Sardinia[56]. Similar studies in Japanese populations identified nine genetic clusters and genetic ancestry shared with Korean and Han Chinese, and genetic components from Central, East, Southeast and South Asia[59]. There are indications that admixtures in populations lead to transfer and retention of genetic variants with specific functions relating to health and fitness[58].

The genetic variation in populations has the potential to confound studies attempting to identify risks of diet- and lifestyle-related diseases and likewise dietary interventions to maintain health and prevent disease. Accessing data on allelic variants from the genome-wide association studies has the potential to generate novel insights into genetic markers of disease risks that may be used to stratify study populations to develop improved dietary interventions to maintain and prevent diet-related diseases. However, this will entail careful analyses and development of robust approaches to select ancestry informative markers and avoid introducing spurious associations[55,60]. In Scotland researchers set up the Generation Scotland: Scottish Family Health Study to compile detailed genotyping and linked phenotypes. Kerr *et al.*[60] established validated procedures for accurate data collection and associated quality genetic data with low error rates. This study also raised concerns about pedigree (ancestral phenotypes conferred by specific genes) inconsistencies, which are a hidden confounder in studies which do not record genetic information in parallel with phenotyping data[60,61].

Population diversity, perceived or genetic, is a significant factor in designing experimental studies and interpreting results. Advances in gene sequencing and improvements in accuracy and analyses bring us closer to identifying DNA variants that determine disease risk and our responses to nutrition. There have been reports of various DNA loci (genetic markers) associated with many of the markers routinely measured to assess responses to nutrition and prevention or improvement in disease outcomes[10,25,62–64]. The task is challenging, with researchers identifying large numbers of DNA variants associated with markers routinely measured in nutrition research. Over 250 loci have been identified linked to BMI and further analysis identified protein-coding variants linked to neuronal pathways and eight novel gene targets implicated in human obesity[65]. Blood lipids are common targets to assess disease risk and the impact of dietary interventions. However, ninety-five genetic loci have been reported to influence blood lipid levels in individuals of European ancestry[63]. Further metabolomic profiling of lipoproteins, lipids and metabolite variables elucidated underlying biological processes associated and specific lipid:gene effects[64]. Inflammation is also a focus of nutrition research and the marker C-reactive protein is routinely measured. Studies have highlighted genetic variants associated with elevated C-reactive protein when intake of TAG and cholesterol are increased[6]. The same genetic variants were associated with anti-inflammatory responses to high *n*-6:-3 ratios[6]. It was also identified that carbohydrate influenced C-reactive protein associated with DNA variants via effects linked to HbA1C and fasting glucose levels[6]. Knowledge of genetic ancestry and trans-ethnic analyses of genome-wide association studies has revealed novel loci associated with commonly used markers in nutrition research including, glycated haemoglobin (HbA1c)[10], fasting glucose and insulin[66].

SNP genotyping of DNA variants has the potential to inform approaches to formulating nutritional advice on intake of nutrients. SNP that determine absorption and metabolism of nutrients indicate that this could inform dietary requirements for sub-populations and individuals[67]. SNP-genotyping studies in a New Zealand

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population self-reported as having European ancestry identified SNP variants within this population that were associated with Se status[67]. This supports genetic testing of populations in parallel with race and ethnicity coding and supports previous evidence that Se requirements in human subjects varies with genotype[68]. Despite the profound implications of genetic variation in human subjects there is still a scarcity of nutritional studies identifying, testing and reporting common DNA variants. The Human Variome Project[69] was set up to compile information on genetic variation and facilitate future application in genetic healthcare. It may be that a similar global initiative is required to compile the necessary data from nutrition research and collaboratively develop resources and information to facilitate a global evidence base.

Sex as a biological variable and distinguishing from gender

A variable that is easier to control and incorporate in nutrition research is sex. It is over a century since Nettie Stevens's[70] seminal paper identifying the significance of the XX and XY chromosomes. The presence of an XX or XY chromosome influences disease risk and many of the markers that are measured in response to nutrition[71–74]. Despite this knowledge, sex as a biological variable (SABV) has not retained the prominence in nutrition studies that it deserves[75–79]. Studies of diet- and lifestyle-related diseases and dietary considerations to prevent them often do not reflect this most obvious variable, or it is considered as a confounding factor rather than a factor worthy of empirical and systematic research[5,79]. Biological research, including nutrition studies, are predominantly conducted in males, with results erroneously extrapolated to females[5,80–82]. If mixed cohorts are studied, there is often a failure to report SABV[5,80–82].

Addressing SABV in nutrition research is thus important and requires consideration in approaches to study design, analyses and reporting. To tackle these approaches appropriately, it is necessary to firstly clearly distinguish sex and gender, which are often used erroneously in the scientific literature[78,83–85]. Sex differences are associated with biological factors attributed by the presence of XX or XY chromosomes[71,86–88]. In contrast, gender is associated with various behaviour, lifestyle and cultural experiences as opposed to biological factors[89]. Thus, both biology and behavioural differences may impact the risk of diet- and lifestyle-related diseases and responses to dietary interventions and the crucial differences require sex and gender specific approaches[90–92]. Alternatively, integrated frameworks are required to study interactions between sex, gender, genetics, health and nutrition[76,79]. Genetic variants and health outcomes are connected to social and cultural variation factors and a multisystems approach is necessary to decipher the interaction of sex and gender in physiological and behavioural responses[76,79,82,92].

The lack of studies conducted on empirical and systematic sex differences has promulgated male dominated research that has limited applicability to address physiology and pathophysiology in biological systems regulating food intake, bioavailability and utilisation in human populations[5,93]. This prompted the National Institutes of Health to form the Office for Research on Women's Health in 1990 to promote research to appropriately address SABV. The European Institute of Women's Health was set up a few years later in 1996 with the aim of promoting gender equity in the European Union (EU) funded research on female and male biological differences and gender roles linked to health. The European Institute of Women's Health also sought to lobby at EU and regional levels and interact with other organisations, such as the WHO. This led to a study reporting the need to clearly define sex and gender and strategies to ensure inclusion of sex and gender in research programmes for life sciences[94,95].

The National Institutes of Health announced in 2014, that it would ensure investigators accounted for SABV in National Institutes of Health-funded research. This decision was widely supported, with many publications forecasting greater rigour and advances in biological research[96–98]. Further publications offered insights on methodological approaches that might be considered to ensure integration of SABV in study design and statistical analyses[99].

However, despite attempts to change policy, changes in experimental design and analyses have been slow to address this in human subjects, as well as in animal and cultured cell model systems used in nutrition research. The use of male animal models still predominates[100]. The justification often offered is that data from female animals are more variable than that gathered from male animals, despite studies demonstrating that this is not the case[101–103]. Cultured cell lines are used extensively in nutrition research to study biochemistry, cell signalling and gene or protein regulation in response to nutritional and dietary components. However, the sex of the cells used and differences in cells harbouring XX or XY chromosomes are largely ignored and seldom reported[13,104]. *In vitro* studies often fail to report the XX/XY status of the cell lines used despite evidence that the sex of cells used can impact on the biology of that cell and observed responses[14,105,106]. This is particularly concerning with specific cell lines dominating areas of nutrition research e.g. CACO2 and HEPG2[107,108], both of which carry XY chromosomes. Stem cells are increasingly being used in research[105]. However the culture conditions used favour derivation of female stem cells, leading to much of this research being conducted on cells carrying XX chromosomes[109].

Technological innovations and emerging research fields to address the challenges of inter-individual variation

The application of omic technology platforms has the potential to provide detailed and robust data, which combined with bioinformatics, has the potential to

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characterise individual variation and identify associated biomarkers and nutrition intervention targets[65]. The incorporation of omic technologies, such as genomics, proteomics, metabolomics and epigenetics in nutrition research is elucidating genetic variants, gene, protein and metabolic biomarkers and signatures that may decipher interindividual variation in responses to nutrition and permit identification of determinants of nutritional responses[2,3,28–30]. This has created opportunities for the evolution of new research fields, such as personalised and precision nutrition (nutrition tailored to individual attributes), molecular epidemiology and nutritional bioinformatics[31,32].

However, despite the rapid advances in technologies and their application to studying and characterising the diversity within populations, utilisation of the information gleaned has not proven to be straightforward. The large and complex data collected and the myriad possible interactions between 30 000 human genes[110] and the encoded human proteome consisting of many proteoforms[111], is a challenge for integrated statistics and bioinformatics to analyse and interpret. Meeting this challenge necessitates development of new multidisciplinary teams and acquisition of new skills, expertise and knowledge to drive multi-omic data integration and systems approaches. Integrative multi-omics approaches have potential to advance utilisation of omic data to detect causal genes and DNA variants linked to diet- and lifestyle-related diseases, together with the associated regulatory networks and signalling pathways[24,112]. Advancements are being made in this area to integrate multi-omic data to permit data mining[23,113,114]. This opens the potential to link to electronic health records to identify diet- and lifestyle-related disease markers[27,114]. Disease specific databases of multi-omic studies conducted across different species are being constructed and linked to clinical information[113,115,116]. Biobanks are being developed to link genetic data of intensively phenotyped individuals with electronic health records[27,117,118]. Diet- and lifestyle-related disease multi-omic databases have potential to provide detailed information on biological processes, molecular determinants and potential mechanisms linking diet to disease risk. Such approaches may also be useful in permitting extrapolation of data from studies in animal models to human subjects by permitting assessment of inter species differences[115]. It is now feasible to systematically capture store, manage, analyse and disseminate data and knowledge of nutrient–gene interactions to study specific nutrients and links to human health[10,67,119]. The Micronutrient Genomic Project evaluates micronutrient and health studies, combining genetic/genomic, transcriptomic, proteomic, metabolomic, nutrition, biochemistry and epidemiology to construct pathways and biological networks[119]. Genomics is revealing important relationships of SNP and other DNA variants in the human genome that have implications for nutrition and tackling inter-individual variation[67]. For example, the daily requirement for Se, an essential dietary nutrient, is significantly influenced by the genetic variants in the genes encoding selenoproteins[67]. Gene signatures have potential to stratify study populations and aid interpretation of inter-individual variation in study groups[2,3]. Ultimately, such developments will make it feasible to incorporate diverse individuals and populations that currently do not meet inclusion criteria for recruitment currently used to compile study cohorts for nutrition research.

Science policy and reporting strategies to address the challenges of inter-individual variation

Organisations funding nutrition research, learned societies, nutrition researchers and the scientific and academic literature all have the potential to impact on the challenges of the heterogeneous nutrition response. The NIH and EU polices to incorporate sex and gender perspectives have initiated concepts within science funding, study design and analyses and reporting[80,84,94,96,120,121]. However, progress has been slow and improved tracking of the incorporation of these biological and behavioural variables needs to be more closely monitored with further incentives warranted. Research funders' stipulation that research scientists account for sex and gender aspects in their research proposals is partly reliant on reviewers, who are often not alert to sex and gender variables. Similarly, attempts to improve race and ethnicity coding are dependent on researchers acknowledging and reporting the limitations of race and ethnicity coding. This also applies to peer review of scientific literature. Prominent scientific journals have introduced Editorial policies for reporting SABV[81]. The International Committee of Medical Journal Editors compiled their Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, with updates produced in December 2018[122]. Likewise, Sex and Gender Equity in Research guidelines were developed by The European Association of Science Editors for reporting sex and gender in all types of science publications[123,124]. Animal Research: Reporting of *In Vivo* Experiments guidelines published by the National Centre of the Replacement, Refinement and Reduction of Animals in Research aim to improve the standard of reporting, including SABV[125]. While the issue of female/male equality in research has been gaining prominence there is still a lack of awareness of the issues surrounding sex/gender perspectives in research and a lack of consistency in reporting research from a sex/gender perspective[76]. The Gendered Innovations project[126] is tackling this issue on various fronts. Sex and gender interactions in nutrition research are being investigated to address application of the ubiquitous diet assessment tool, the FFQ[127] and NCD and gender[128,129] are being studied. Gender scoring is being developed to address eating-related pathologies[130].

Future advances in nutrition research are dependent on a coordinated approach to address the challenges of the heterogeneous nutrition response. Indeed, the emerging fields of molecular epidemiology, personalised/precision nutrition depend on identifying determinants of

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inter-individual variation. Although the fields of molecular epidemiology, personalised/precision nutrition are relatively young, emerging evidence for scientific validity of nutrigenetic knowledge is gathering focus with frameworks for application in tailoring dietary recommendations to better address stratified sub-groups and individuals[131]. Improved technologies generating robust genetic information and increased understanding of the genetic basis of complex NCD is paving the way to incorporate genetic risk scores in studying NCD[22,82,132]. The challenge of addressing perceived race and ethnicity and associated risk of NCD may also be advanced through identification of genetic determinants[10].

Nutrition researchers have a fundamental role in addressing the heterogeneous response. Together with incentives from research funders and scientific publishers, scientists have the possibility to address the challenges of inter-individual variation by accounting for variables, such as sex in study design and analyses. Furthermore, as reviewers of research proposals they can support unbiased reporting. Simple measures, ensuring that *P* values are not misused[12]. Variation and the extent between sexes and variation within study groups should be reported using appropriate statistical methods, an essential requirement to interpret reported group means. The compilation and application of guidelines for sex and genetic scoring, with improved coding of race/ethnicity and gender, should be encouraged at early stages of developing careers in nutrition science. This should include appreciation of novel statistical approaches to address the challenges of omics data and wider application in interpreting data gathered from heterogeneous nutrition responses[133].

Conclusions

This review is by no means a comprehensive treatise on the heterogeneous nutrition response. The necessity to summarise this broad topic uncovers the iceberg tip of the challenges facing nutrition scientists in addressing the heterogeneous nutrition response. However, continuing to avoid these challenges is not an option if nutrition science is to progress. Tackling the heterogeneous nutrition response is necessary to improve dietary guidelines and reference values that are appropriate for both populations and individuals, to prevent diet-related diseases and provide improved dietary advice for healthy ageing. Action is called on for several fronts to incorporate diversity as an important biological variable. Diversity blindness must be erased from nutrition research to avoid hindering identification of the mechanisms and determinants of responses to nutrition. This is necessary to progress nutrition science, to formulate sound dietary advice for both populations and individuals and provide novel targets and approaches to tackle the rising swell of NCD and unhealthy ageing. A coordinated approach from funders, learned societies, nutrition scientists, publishers and reviewers of the scientific literature is necessary to improve race/ethnicity/genetic/sex and gender coding. This is a prerequisite to incorporating population diversity in all aspects of nutrition. This includes study design of basic, pre-clinical and clinical research and promoting improved reporting and reviewing of nutrition research.

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