The Economist Intelligence Unit

IMPROVING NUTRITIONAL GUIDELINES FOR SUSTAINABLE HEALTH POLICIES

A report by The Economist Intelligence Unit

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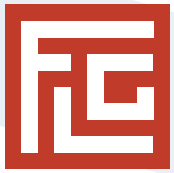

This paper examines the themes raised at an international meeting convened and organised by the Fondazione Giovanni Lorenzini Medical Science Foundation (Milan, Italy – Houston, TX, USA) on 'Improving nutritional guidelines for sustainable health policies'. These themes were further explored through identifying relevant literature and interviews with presenters and attendees of the meeting. The discussion paper was sponsored by the Fondazione Giovanni Lorenzini Medical Science Foundation, a charitable foundation. It is a product of the effort from The Economist Intelligence Unit.

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Executive summary

The Economist Intelligence Unit (EIU) was invited to attend a recent international meeting organised by the Fondazione Giovanni Lorenzini Medical Science Foundation (Milan, Italy – Houston, TX, USA) on improving nutritional guidelines in order to create sustainable health policies. This discussion paper further explores emerging themes from the presentations and discussions during the meeting, through follow-up interviews supplemented by selected literature.

Guidelines understandably dominated discussion at the meeting. However, the limitations of the underlying primary research also provided much debate. The main themes to emerge from the day were around ways in which guidelines can reflect the state of the evidence, how guideline producers can identify and manage conflicts of interest, the challenges facing primary research in nutrition and innovations in nutrition science.

Based on these emergent themes, we extracted key ideas for future action, which are explored in greater detail in the discussion paper:

KEY IDEAS FOR FUTURE ACTION	
Include everyone	Nutrition requires cross-disciplinary collaboration and input
Overcome challenges	Primary research in nutrition is challenging but there are solutions
Manage conflicts	Conflicts of intrest can be identified, mitigated and managed
Digestible guidelines	Guideline recommendations must make sense to all their users
Think implementation	Guidelines must be practical and implementable

Nutrition is much more than just the science of how much of any nutrient individuals should consume. To meaningfully impact on health, the input of various other professionals is needed to ensure that all aspects of adherence and practicality are considered in primary research and guidelines, which is why you need to *include everyone*. Whilst undertaking primary research in nutrition is challenging and there are limitations to the research methods used, there are solutions and ways to overcome these limitations. Similarly, conflicts of interest are a particular challenge in nutrition because so much research is funded by industry, but this is also the case for other fields – so there are ways to work around this, hence the need to *overcome challenges*. Guidelines in particular need to be understood by those who use them – both the physicians 'prescribing' them and the general public trying to implement them into their lives. Guideline developers therefore need to produce *digestible guidelines*. Following on from this, guideline producers also need to think about practical, implementation-related issues to ensure that their scientifically sound guideline translate into changes to people's habits and improvements in their health. Therefore, throughout the process they need to *think implementation*, rather than risk it being an afterthought.

These key ideas for future action are explored in more detail throughout this discussion paper. Superficially these may seem rather generic, but that is precisely the point. The discussions during the meeting and subsequently indicate that there is some uniqueness in the way that these challenges present themselves and interact within nutrition research. However, the challenges in themselves are not unique. This provides the nutrition research and guideline community with an opportunity to look to other disciplines that have faced these challenges and learn from how they have tackled them.

Based on our observations from attending the meeting and subsequent discussions, we feel that there is some risk of collective defeatism in the face of the challenges that nutrition researchers and guideline producers face. These challenges are real and present for the nutrition community, but no more or less surmountable in nutrition than elsewhere. The true challenge is in being open to finding ways to overcome and mitigate these challenges.

Glossary

Biomarker	A biomarker is a natural molecule, gene, or functional characteristic by which a specific physiological or pathological process can be identified. They are commonly used to diagnose conditions and to assess how advanced an individual's illness is.
Conflict of interest	An interest that may affect an individual's ability to impartially assess the evidence or provide a perspective on a particular topic. Conflicts can be financial – where the person is in direct or indirect receipt of financial support, or intellectual – where the person may have a reputation built upon a particular stance on an issue.
Diet	Diet is the sum of food and drink, consumed by an individual and often implies its quality, composition and effects on health.
Dietary or food-based guidelines	Translate nutrition guidelines into foods using non-technical language, enabling individual consumers to compose their daily diet in a way that provides the appropriate nutrition.
Feasibility/ implementation	Considers how health policy will be implemented, including assessing and mitigating any individual, social, cultural, economic and practical barriers to implementation. For example not recommending food sources of nutrition that the majority of the population may not be able to access due to financial constraints or availability.
Food	Food consists of essential body nutrients, such as carbohydrates, fats, proteins, vitamins, or minerals, which are ingested and assimilated by an individual to produce energy, stimulate growth, and maintain life.
Guidelines	A series of recommendations on a particular topic (e.g. health condition or aspect of health, such as nutrition), developed by a multidisciplinary panel based on an independent systematic review of the best available evidence. Guideline panels can include health professionals and academics specialising in that area, as well as representatives of other groups such as the general public, the policy makers, and the industry.
Nutrition	Nutrition interprets the interaction of nutrients and other substances in food in relation to the linked metabolic effects within the body. It includes food intake, absorption, assimilation, metabolism, and excretion.
Nutritional guidelines	Nutrition guidelines focus on the quantities of individual nutrients and quality/quantity of whole foods that people should consume to achieve a healthy nutritional state. These usually apply to the entire healthy population, using broad groups – such as different age bands – but can also be tailored to more focused population groups. Nutrition guidelines include estimates such as dietary reference values (DRV), reference intake, and daily intake. The general public often come into contact with these when examining food packaging which may have DRVs on the front etc.

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Policy makers	Professionals working within local and national government that are responsible for translating research findings into actionable health policy to promote health in their population. For example, creating food-based guidelines based on nutritional guidelines, the best available evidence and stakeholder input.
Randomised controlled trial	A randomised controlled trial (RCT) is a clinical study with a specific design aimed to reduce bias when testing a new treatment. Subjects participating in the trial are randomly allocated to either the group receiving the treatment under investigation or to a group receiving standard treatment (or placebo treatment) as the control.
Substitution effect	When advised to eat less of one nutrient (e.g. carbohydrate) or individual food, the public will substitute that item with another. Substitution advice should be provided to ensure healthy substitutions that do not have unintended harms.
Surrogate disease biomarker	In some research areas, it may be challenging to conduct studies that are sufficiently long-term to wait for disease outcomes (such as heart attack) or answers may be required in the meantime. In such cases, biomarkers of that disease (e.g. blood pressure) can be measured to predict the likely risk of later developing the disease. However, these results indicate a possible risk rather than providing direct causal proof.
Weak/qualified/ conditional recommendations	Where evidence is limited, in terms of its quality or quantity, this affects the level of certainty in any conclusions based on that evidence. Describing recommendations as weak, qualified or conditional communicates this level of uncertainty.

Introduction

In the twenty first century, nutrition remains a global health priority but is changing. The World Health Organization's (WHO) second sustainable development goal is to "end hunger, achieve food security and improved nutrition and promote sustainable agriculture"(WHO, 2015). World hunger remains a challenge that requires this global attention. However, although much of the world has theoretical access to adequate nutrition, this does not always translate into actual access, hence the WHO's focus on ensuring food security, for example to prevent food price instability making foods unaffordable. According to the WHO, obesity levels are rising and most of the world's population live in countries where more people are dying due to overweight rather than underweight (WHO, 2016b). But of course taking in more food does not mean that people are taking in more nutrients. There is increasing concern about the intake of energy-dense-nutrient-poor foods that are often highly processed, cheap and palatable, providing people with their energy intake but little nutritional value.

Step forward nutritional guidelines to try to address inadequate nutrition. Whether in the context of a lack of or excess of food, nutritional guidelines provide a scientific basis for action. Policy makers translate them into food-based dietary guidelines to advise consumers on how to compose a diet that will deliver the necessary nutrition. Health professionals use nutrition and dietary guidelines to in turn advise their patients.

The Economist Intelligence Unit (EIU) was invited to attend a recent meeting organised by the Fondazione Giovanni Lorenzini Medical Science Foundation (Milan, Italy – Houston, TX, USA) on improving nutritional guidelines in order to create sustainable health policies. Participants at the meeting highlighted an array of on-going issues in nutrition research that extend to the development of nutrition and dietary guidance, impacting on the regulations or policy based on these.

The reliance on observational studies, the need to live with small effects and difficulties in drawing the evidence together in systematic reviews were all highlighted at the meeting. This presents a frustration for non-research stakeholders such as guideline developers, policy makers and regulators. These groups want to base recommendations or policy on high level evidence but often need to live with weaker recommendations. Statements that are less certain may be useful for clinicians but often are not sufficient for national level policy or regulation, and may be difficult for the public to interpret.

Where recommendations are "weak" or "conditional", how can this be communicated to the public in a clear way without diluting the message? How can citizens be reassured that policy and regulations are firmly based on reliable evidence and take into account the views and preferences of individuals and populations?

The meeting acknowledged that nutrition research is, in some ways, different to clinical research. There were abundant views expressed at the meeting on what could be considered to improve primary research processes. Consideration of the special features in developing nutrition guidance from systematic reviews led to constructive suggestions for their improvement.

Good nutrition is vital at all stages of life, but has an especial impact around the time of and during pregnancy. Current advice on healthy nutritional intake can cater for specific groups such as pregnant women, but is there more that could be done to personalise and potentially improve nutrition advice? The meeting included the presentation of innovative research and discussion of the potential future direction of nutrition advice. So what can be done to support these new discoveries in nutrition and to improve the confidence in nutritional research?

The scope of this project was focused on nutrition guidelines, but inevitably there is cross-over with food-based dietary guidelines. Nutrition guidelines focus on the quantities of individual nutrients that people should consume to achieve a healthy nutritional state. Whereas dietary guidelines translate nutrition guidelines – such as dietary reference values – into foods, to enable individuals to compose their daily diet in a way that provides all the necessary nutrients.

The goal of this project is to produce a thought-provoking discussion paper that will explore how high quality nutritional and dietary guidance can be developed that is appropriate and tailored to individuals and groups within populations, as well as geography, religious, agricultural and economic considerations.

"There's more uncertainty in nutrition dogma than people are willing to admit" - Dennis Bier

Methods

Identification of key themes

The presentations and discussions at the international meeting held by the Fondazione Giovanni Lorenzini Medical Science Foundation provided the key themes that were the foundation for this discussion paper.

The five key themes that emerged from the international meeting were:

1. How can guidelines reflect the evidence
2. How can conflicts of interest be identified and managed
3. How policy makers use guidelines
4. How nutrition science is different
5. Innovations and looking ahead in nutrition science

These findings were complemented by two broad strands of research: interviews with key opinion leaders and focused literature searching.

Interviews with key opinion leaders

A series of in-depth interviews and responses via email were used to gather the views of stakeholders amongst the delegates at the international meeting. Interviewees were identified for each of the themes emerging from the meeting (see above) based on their experience and knowledge. We tried to ensure that our interviewees were a broadly representative sample of the participants, including policy makers, clinicians, scientists and methodologists.

We engaged the following participants from the meeting:

1. Arne Astrup, Professor Department Nutrition, Exercise and Sports University of Copenhagen, Copenhagen (Denmark)
2. Dennis M. Bier, Professor of Pediatrics and Director USDA/ARS Children's Nutrition Research Center Baylor College of Medicine, Houston TX (USA)
3. Furio Brighenti, Full Professor and Chair of Human Nutrition Department of Food Sciences University of Parma, Parma (Italy)
4. Luigi Fontana, Professor of Medicine and Nutrition - Department of Clinical and Experimental Sciences, Brescia University; Department of Medicine, Washington University in St. Louis, St. Louis MO (USA)

5. Robert Gibson, Professor of Functional Food Science, The University of Adelaide, Adelaide (Australia)
6. Ranieri Guerra, Director General for Preventive Health Ministry of Health Italy, Rome (Italy)
7. Gordon Guyatt, Distinguished Professor Department of Clinical Epidemiology & Biostatistics McMaster University, Hamilton ON (Canada)
8. John Ioannidis, C.F. Rehnborg Chair in Disease Prevention Professor of Medicine and of Health Policy and Research, Stanford University, Stanford CA (USA)
9. Maria Makrides, Theme Leader Healthy Mothers Babies and Children South Australian Health and Medical Research Institute, Adelaide (Australia)
10. Basil Mathioudakis, Basil Mathioudakis Consulting - Food legislation and nutrition, Brussels (Belgium)
11. Chirag Patel, Assistant Professor of Biomedical Informatics Department of Biomedical Informatics Harvard Medical School, Boston MA (USA)
12. Holger Schünemann, Chair Department of Clinical Epidemiology & Biostatistics Professor of Clinical Epidemiology and Medicine McMaster University, Hamilton ON (Canada)
13. Raanan Shamir, ESPGHAN President, Chairman Institute of Gastroenterology, Nutrition and Liver Diseases Schneider Children's Medical Center of Israel Professor of Pediatrics Sackler Faculty of Medicine Tel Aviv University, Tel Aviv (Israel)
14. Niv Zmora, PhD candidate at Elinav Lab Immunology Department Weizmann Institute of Science, Rehovot (Israel)

The interviews and questions focused on the key theme most relevant to the interviewee's experience and knowledge, but also touched on overarching themes such as challenges in producing guidelines in nutrition. Interviews were semi-structured to allow the interviewer to follow up points made by the interviewee and to ask them about other topics.

Direct quotes from interviewees are presented in double speech marks and italicised. Quotes such as turns of phrase are presented in single quotation marks without italics.

Focused literature searching

The key themes and findings emerging from the interviews were supplemented with focused literature searching to understand their context. Sources included the biomedical database PubMed and the websites of key policy organisations, such as the WHO to retrieve "grey literature" – guidance, policy and other documents not published in formal journals. Additionally, presentations from the meeting were reviewed for additional content and references. The literature searches were pragmatic and focused, and not designed to be comprehensive.

Analysing data

The themes from meeting presentations and discussions provided the foundation for interview questions and analysis, although we developed and refined the themes iteratively as the analysis progressed. This approach enabled the continual exploration and refinement of themes.

The contents of the presentations given at the meeting and the plenary discussions, the findings of the literature review and stakeholder interviews were combined to generate a narrative around the key ideas for future action. The themes originally emerged as questions, but they are presented in the findings section as statements that reflect and summarise our findings.

Findings

Guidelines could better reflect the evidence

The limitations of primary research in nutrition were a hot topic at the meeting. The weakness of much of the available primary research inevitably weakens the quality of guidelines and the strength of recommendations based on this evidence. There was also an acknowledgement of the methodological inadequacies of some past nutritional guidance, where there was an overuse of expert opinion and underuse of available (albeit limited) evidence. This use and abuse of evidence in guidelines was the biggest theme at the meeting.

When to develop guidelines? – "It has to have academic and scientific interest…But there has to also be a public health interest" – Ranieri Guerra

The prompt for developing nutrition guidelines should be a public health need. Indeed, Arne Astrup, Professor in the Department Nutrition, Exercise and Sports at the University of Copenhagen, emphasised that guideline developers must remember the purpose of nutrition and dietary guidelines – to be useful and understandable by the physicians 'prescribing' these diets and the public – and that developing guidelines is not merely *"an intellectual game among scientists"*.

Luigi Fontana, Professor of Medicine and Nutrition, Brescia University and Washington University in St. Louis, stressed the need to define the goals of guidelines at the outset. The role of the funding body can influence the focus of the guideline, potentially steering it away from that public health need. Defining goals may help to mitigate this influence. It can be challenging in the field of nutrition to achieve non-partisan funding for guideline production and syntheses of the evidence. Holger Schünemann, Chair of the Department of Clinical Epidemiology & Biostatistics and Professor of Clinical Epidemiology and Medicine at McMaster University, highlighted that in nutrition research in particular, there is emphasis on new technology rather than synthesising and appropriately communicating the current best evidence. Therefore the availability of funding for a guideline, and the assessment of genuine need, is often not aligned.

The decision about when to update guidelines was equally vexed. Ranieri Guerra, Director General for Preventive Health at the Ministry of Health in Italy, felt that there was less interest in updating guidelines than there was in producing them. This is common across most fields of guideline production. Gordon Guyatt, Distinguished Professor in the Department of Clinical Epidemiology & Biostatistics at McMaster University, noted that people were beginning to understand that guidelines cannot be static until their next update two or more years later and that a more dynamic approach to updating guidelines is needed. The consensus was that guidelines should be updated when there is

new scientific evidence that either potentially contradicts or changes recommendations. However, who is going to run and fund the on-going horizon scanning process to ensure that new evidence is logged, assessed and appraised?

Guidelines should follow a high quality process, so why aren't they? – "Change is hard, people have ways of doing things, something new comes along and initially there'll be resistance to change" – Dennis Bier

The meeting agreed that the best process, in an ideal world, for developing guidelines is:

1. select a guideline area where there is a need for guidance
2. clearly define appropriate questions
3. conduct systematic reviews (and ideally meta-analyses) to address those questions
4. appraise the evidence
5. consider relevant criteria that influence any recommendations – such as cultural acceptability

Even when following this ideal process, there will be variations in the decisions and recommendations that different nutrition and dietary guideline development groups will reach based on the same evidence. This is partly due to the criteria that guideline committees must consider, which may be specific to the setting to which the guideline is to be applied. The individuals involved in decision-making will also have an influence on the conclusions reached. But interviewees agreed that the most important thing was to get everyone looking at the data in front of them in an unbiased, open-minded way to ensure that nutrition guidelines are as evidence-based as possible.

There was some disagreement among participants about the details of guideline processes but the overall feeling was that the principles of producing high quality guidelines are universal, and not specific to any particular discipline. However, Gordon Guyatt noted that there may be nuances of application, and particular methodological challenges in the nutrition field that guideline developers will be required to address.

In general though, there was widespread consensus that the above guideline process is the preferred approach. Which begs the question: if everyone agrees that the standards for guideline production are good and useful, why did so many people at the meeting report that these standards aren't being followed?

The main reason that emerged would be unsurprising to any student of human nature: resistance to change. People get used to doing things in a certain way that works for them and don't always want to change. Implementing these standards can be challenging in large organisations, where both organisational change and individual change is required.

But there are signs of progress. Holger Schünemann feels that *"good guideline development in the field of nutrition has already happened"*. He gave the example of guidelines that he has been involved

in developing for the World Allergy Organization, which advise on nutritional supplementation for the prevention of allergies (Cuelo-Garcia, 2016, Fiocchi, 2010, Fiocchi, 2015, Yepes-Nuñez, 2016). Another example was the WHO, which was previously criticised for an overreliance on expert opinion in the formulation of its guidance and recommendations (Oxman et al., 2007). In response to this criticism, the WHO overhauled its methodology to bring it into line with international standards.

Professor Guyatt and Schünemann, who are involved in developing standards for guideline production, feel that these guideline standards are being increasingly adopted and were optimistic about their future role in nutrition guidance.

Involving stakeholders – "The problem is that nutrition is too important to leave to nutritionists" – Ranieri Guerra

All agreed that there is a need to ensure that relevant stakeholders and groups are involved with guideline production, and in particular that guideline development panels are drawn from a wide range of professionals. Arne Astrup, Ranieri Guerra and Maria Makrides all specifically stated that the issues involved in nutrition were so broad that people working in nutrition could not necessarily solve them alone.

When bringing together guideline panels academics, scientists and clinicians are all well-established potential panel members. Academics and scientists can bring their knowledge of the scientific underpinning of guidance. Clinicians may or may not understand the science, but certainly do bring experience of implementing the science into clinical practice.

People drawn from the social sciences are sometimes less well represented. However when present they help the guideline development group to understand individual, social and cultural factors that may affect guideline uptake and adherence. For example, Arne Astrup described how the involvement of sociologists in a project he worked on had transformed their understanding of why people weren't adhering to the prescribed diet. The issue was that there had been a marked difference in compliance with protein targets between men and women. Their previous data had only captured that people weren't complying, not why they weren't. Interviews by sociologists revealed that the difference was because the women in the study did not like eating meat in the quantities needed to hit their target. This knowledge meant that the diet could be tweaked to diversify the protein sources, accommodating individual preferences and increasing adherence.

Professor Guyatt made the case for also including methodologists in guideline development. This is to ensure that expert views are moderated and that strong opinions would not override objective guideline development methods. The methodologists would therefore have to be robust enough to stand up to the weight of expert opinion. Finally, Ranieri Guerra felt that it was important to involve the public in guideline development, because they can make a valuable contribution and after all, they are the people expected to follow these guidelines.

But should the guideline development group include *all* stakeholders? Basil Mathioudakis, a consultant in food legislation and nutrition, was clear that the systematic reviews forming the scientific basis for the guideline should be free of *"interference"* from stakeholders, including policy makers and regulators, and that their role comes at a later point in the guideline process. Dr Guerra felt that industry was another important stakeholder and that they too should be involved in parts of the guideline process, in a controlled and managed way. The consensus remained that guidelines *"should be the result of the interaction of all contributors"* (Basil Mathioudakis) regardless of when or the extent to which they contribute.

The overwhelming feeling was that including a variety of stakeholders in guideline development and representing a range of professions in guideline panels will bring to guideline production a range of perspectives, experiences, knowledge and training. Although there were some differences of opinion about just how inclusive the core guideline development group should be – such as the involvement of industry and policy makers.

Finally, Ranieri Guerra called for greater transparency in how guideline panels are selected and convened. The group must be able to fend off the potential criticism that, as he put it, *"whoever convenes the panel has called upon the friends and the friends of the friends"*.

Uncertainties and limitations in the evidence – "How weak is too weak?" – Maria Makrides

Much discussion during the international meeting centred around the various limitations of the primary research that underlies guidelines and how to communicate the limitations of the evidence and the uncertainties these create. The consensus was that guideline producers need to be more willing to communicate this uncertainty by making recommendations that are 'qualified' or 'conditional' or 'weak'. Such recommendations reflect the limitations – in terms of its quality or quantity – of the underlying evidence, which affects the level of certainty in any conclusions based on that evidence. The limitations of much of the evidence in nutrition mean that qualified recommendations are a reality that nutrition guideline producers must reconcile themselves with.

There was no clear agreement on whether there is a cut-off point for when a recommendation can be made, albeit with various qualifications. Professor Raanan Shamir, President of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), warned that the existence of and need for qualified recommendations meant that there was a risk that people would make recommendations when they really shouldn't. Maria Makrides, Theme Leader for Healthy Mothers Babies and Children at the South Australian Health and Medical Research Institute, considered that when making qualified recommendations, panels should be clear on what the 'qualification' is because *"if you can't articulate the qualification, then is it worth making"?*

The public need for guidance on these subjects meant that to not make recommendations was not considered an appropriate solution. The difficulties that guideline panels face in formulating recommendations mean that we cannot expect that most members of the public will have the *"time, energy or skills"* as Gordon Guyatt put it, to appraise the evidence for themselves. Holger Schünemann recommends coming up with the *"best possible answer"*, because the alternative is leaving people at the mercy of messages that are potentially biased and not formulated in a scientific manner.

There was some concern at the meeting about the potential risk to credibility or potential for cynicism amongst the general public if guideline producers make recommendations that subsequently have to be reversed. However, most interviewees seemed to agree that changing recommendations in the face of new evidence was no bad thing. Equally, Professor Schünemann felt there was a risk in *"remaining silent"* under these circumstances and that following a sound methodology reduces the risk of having to overturn guideline recommendations, rather it would entail incorporating new evidence into guidelines and recommendations. He speculated that previous guidelines that have seen such dramatic changes were probably not based on high quality methodologies.

Several interviewees felt that the communication of the uncertainty was inadequate and could be improved by presenting the degree of uncertainty alongside the recommendation. GRADE is an international standard for guideline production, which enables guideline producers to assess and communicate the quality of evidence and the subsequent strength of the recommendation (see Box 1).

Box 1: GRADE guideline production methodology

The Grading of Recommendations Assessment, Development and Evaluation (GRADE, 2016) is an approach to formulating guideline recommendations that incorporates the certainty in the quality of the evidence and translates this into the strength of the recommendation (Balshem et al., 2011, Andrews et al., 2013). GRADE has been refined over the past sixteen years and is now adopted by many leading guideline producers and is used in all Cochrane Systematic Reviews.

GRADE involves assessing the quality of the body of evidence underpinning a recommendation, rather than the quality of individual studies(Balshem et al., 2011). The evidence is rated as high, moderate, low, and very low, based on an assessment of the risk of bias. The criteria used cover imprecision, inconsistency, indirectness of study results and publication bias. The body of evidence can be downgraded, for example if there is a serious risk of bias, or upgraded where features increase confidence such as a large effect size. The quality rating indicates the certainty about the estimate of effect based on the evidence.

The quality of the body of evidence informs the strength of the guideline panel's recommendation (Andrews et al., 2013). However, this is not a simple equation that low quality evidence leads to weak recommendations. A strong recommendation can be made based on low quality evidence, for example where it indicates a benefit in a life-threatening situation and there is evidence (high or low quality) that there are not harms associated with the treatment.

"Instead of admitting that there are weaknesses and things that we don't know, we take a vote in the room about whether or not we should say this or that" – Arne Astrup

When faced with uncertainty in the evidence underlying recommendations, most interviewees did not feel that guideline producers should shy away from acknowledging this by saying *"maybe rather than absolutely"* (Dennis Bier). Indeed, Holger Schünemann was very clear that the challenges in conducting nutrition research that leads to a high level of certainty should not mean that *"we pretend to be more certain in the research that typically would leave us with uncertainty"*. Guidelines are the synthesis of the best available evidence at the time and will change as new evidence emerges. Indeed, Gordon Guyatt recently sat on a guideline panel where the majority of recommendations were conditional, but did not feel that this made the guideline any less useful in providing an indication of the course of action people should take.

Furio Brighenti, Full Professor and Chair of Human Nutrition Department of Food Sciences at the University of Parma, also raised the issue of applying data from a study in one country to another when formulating guidelines. For example a lot of large-scale nutrition studies are carried out in the United States, but he questioned the applicability of these findings to other countries. This is another aspect of uncertainty that needs to be communicated in guidelines.

Communicate the uncertainties involved in making recommendations based on assumptions/markers – "They show a probability, not a real risk of effect" – Furio Brighenti

The reliance on markers of disease which may indicate the risk of developing a disease, rather than actual disease outcomes, came up a lot in the context of primary research and the challenges in conducting high quality studies. Often researchers cannot follow a group of people for 30 or more years to see if they develop a disease, so instead use markers of that disease (e.g. blood pressure) to predict the likely risk of later developing the disease. Such studies *"show a probability, not a real risk of effect"* (Furio Brighenti) and the markers used may not necessarily be on the *"direct causal pathway"* (Dennis Bier), thus even further limiting the certainty guideline producers can have in those findings. This is another layer of uncertainty that guideline producers need to communicate when making recommendations.

Arne Astrup described looking back at nutritional and dietary advice he had been involved in formulating, which he admits are now wrong. He tried to unpick where they went *"wrong"* in the process, deciding that it was because their conclusions had been based on certain assumptions, which turned out not to be true because the links were later found to not be causal. Bob Gibson echoed this, describing how accumulating evidence had challenged the *"lipid hypothesis"* that had become widely accepted as fact and even dogma. This highlights that our conclusions are only ever as good as the evidence we have to hand at that moment.

Conclusions

- Guidelines should be developed when there is a public health need and updated when new evidence may change recommendations.
- There are international standards for producing high quality guidelines that can and should be used. Individual and organisational resistance to change may be an issue, but there has been an increase in the use of these standards.
- Involving stakeholders in guideline production ensures that different considerations and perspectives are incorporated.
- Evidence that is limited, in quality or quantity, impacts on guideline recommendations. The solution is to make recommendations that acknowledge and communicate the uncertainty this creates, whilst still delivering a clear message to guideline users.

Conflicts of interest should be acknowledged and actively managed

Aside from the challenges of conducting high quality primary research and translating those into guidelines, the next biggest discussion point was how to identify and manage conflicts of interest. This involves treading a fine line between not ignoring conflicts of interest, but also not overstating them.

"What is not appropriate is to make the claim of – everybody is too conflicted, we just have to accept that we're going to have conflicted guidelines" – Gordon Guyatt

Conflicts of interests can be defined as "a set of conditions in which professional judgement concerning a primary interest [...] tends to be unduly influenced by a secondary interest" (Thompson, 1993). There are two broad types of conflict of interest: financial and intellectual. When thinking about conflicts of interest, the tendency is to focus on the financial. However, intellectual conflicts of interest can be equally pervasive and affect people's ability to objectively contribute to producing a guideline.

Financial conflicts of interest are the most obvious and easily declared and identified – receiving money for speaking at conferences, industry sponsorship for studies, receiving a salary, honoraria or holding company shares. Although not unique to nutrition, the high levels of industry involvement with and sponsorship of research make financial conflicts of interest common. Indeed, Holger Schünemann felt that it was important not to forget that *"it's not only the science that is supported [through funding studies] but there is a lot of direct financial conflict of interest"*. Everyone was keen to see declarations of conflict of interest published prominently.

Dennis Bier, Professor of Pediatrics and Director of the USDA/ARS Children's Nutrition Research Center at Baylor College of Medicine, felt that most conflict of interest guidelines focus only on financial gain, but rarely on intellectual conflicts of interest or allegiance biases, where someone's entire career and reputation may be dependent on a particular thesis. The issue, he argues, is partly the perception that *"I didn't get money for this, I'm a balanced party in this committee"*. However, these deeply held, even *"fanatical"* opinions – sometimes based on limited evidence – *"abound"* in nutrition according to John Ioannidis, C.F. Rehnborg Chair in Disease Prevention and Professor of Medicine and of Health Policy and Research at Stanford University (Ioannidis, 2013). These views can sway the recommendations these intellectually conflicted individuals may want the guideline committee to make. Again, Professor Bier described the feeling many have that they can predict what conclusions the committee will reach simply by knowing who is on it. These allegiance biases can apply to entire guideline committees, who Arne Astrup says can feel *"locked in"* by their previous recommendations. Rather than looking at new research to improve understanding and eliminate previous mistakes, he adds, they defend previous recommendations *"as if it was their own honour"*.

Intellectual conflicts of interest may seem more challenging to identify than financial conflicts. However, Holger Schünemann suggests otherwise, stating that reviewing what people have publicly said in the past, the grants they have received and areas of work can highlight key intellectual conflicts of interest, as well as self-disclosure mechanisms such as those used for financial conflicts of interest. The question then is how to manage these conflicts between the *"believers"* and *"non-believers"* (Ioannidis, 2016a).

The World Health Organization (WHO) recently held an expert discussion about conflicts of interest, specifically in light of implementing the nutrition-related sustainable development goals (WHO, 2016a). The conclusion of this meeting was that it is preferable to prevent conflicts of interest wherever possible. Where prevention is not possible some examples of management approaches include disclosure of conflicts, divestment (such as selling company shares), screening panel members prior to recruitment, and recusing or prohibiting panel members from discussions where a conflict exists (WHO, 2016a). Professors Guyatt and Schünemann, through their years of involvement in guideline production and the setting of international standards, had a lot to say about the ways that conflicts of interest can be managed (see Box 2).

Box 2: Strategies for managing conflicts of interest

Professors Guyatt and Schünemann described two key approaches to manage potential conflicts of interest:

1. Using a non-conflicted panel to develop the guideline and its recommendations. Then convene meetings with other experts who may be conflicted so that the panel can gather their views and benefit from their expertise. The non-conflicted panel can then use the views of those conflicted experts to inform the guideline development in a managed way to ensure that the recommendations are not unduly influenced.

2. Having conflicted experts on the panel involved in discussions but recuse themselves from the decision-making process around recommendations for which they have a conflict of interest. To be successful, this approach needs a majority of panel members to be unconflicted, to ensure it is still quorate to reach a decision.

These approaches have been used by various guideline producers and seem to help them to deal with the problem of conflicts of interest. Like other aspects of guideline production, this approach is not unique to nutrition and there are many other areas where there are very few non-conflicted experts available for guideline panels, so there are lots of lessons that can be learned from others' experiences.

Although Holger Schünemann does advise that the degree of conflict should be assessed somehow, because people may appear to be very conflicted on paper but those potential conflicts may not have a bearing on their decision-making. The WHO suggested establishing conflict of interest units to assess the extent of conflict, so that the decision is independent and impartial (WHO, 2016a). There are genuinely conflicted people who should not be included in making recommendations, but blanket exclusion of anyone with any potential conflict is not a sustainable way forward.

The WHO also suggests pluralism – including a wide range of interests and perspectives to dilute the influence of a potentially conflicted individual (WHO, 2016a). But this strategy can be risky if the conflicted individual is powerful and may still overwhelm others.

The main message is that conflicted individuals or organisations (such as industry) must not be involved in the decision making around recommendations. However, they can provide useful input to other parts of the process as long as this is managed appropriately. The challenge being that the decision-making is precisely when everyone wants to be involved.

Conclusions

- Both intellectual and financial conflicts of interest need to be identified and managed, to mitigate undue influence.
- There are ways to manage conflicts of interest, for example allowing potentially conflicted individuals selective input by contributing to the discussion but not the decision-making.

Include policy maker and implementation perspectives in guidelines

Policy makers work in local or national government, and often translate abstract research into health policy that can be implemented to improve the health of the population they serve. For example creating food-based guidelines for members of the public can follow, based on scientific guidelines on nutritional intake. The consensus was that policy maker involvement in producing nutrition and dietary guidance is, at best variable and, at worst inadequate. This was not simply policy makers wanting to secure themselves a place at the table, but reflects a genuine concern that their perspectives are not incorporated into guideline production.

Consider implementation – "It's no good having a biologically sound diet that can't be implemented" – Arne Astrup

The main benefit of involving policy makers in guideline production is their knowledge and experience of guideline implementation. The feasibility of a guideline is dependent on the assessment and mitigation of any potential individual, social, cultural, economic and practical barriers to implementation. For example Ranieri Guerra described the challenge for policy makers when trying to implement a guideline that turns out to be socially or culturally unacceptable. The WHO also recommends that dietary guidelines are evaluated not only on their nutritional content, but also practical factors such as availability, affordability and cultural acceptability that may impact on take-up (WHO, 2003). Both Arne Astrup and Niv Zmora described also considering the availability of recommended food sources of nutrition, in their clinical trials. The involvement of policy makers in guideline development would help to ensure this real-world perspective is incorporated from the outset.

When presented with a new piece of guidance on a particular nutrient, for example, as a policy maker Dr Guerra immediately convenes a meeting of various stakeholders to enable him to understand the *"feasibility, relevance, acceptability"* of the guidance before he designs a policy to meet the guidance. Although he felt that policy makers were not currently involved enough in guideline development, simply sitting policy makers on guideline panels was not a solution to this issue. For him, what was needed was a way to bring the real-world perspective that policy makers have – from translating guidelines into actionable policy – to inform how guidelines are produced and presented, to ensure that they have both high scientific interest and public health impact. Further information on this topic is included in the section on how policy makers use guidelines.

Giving nutrition information in digestible chunks – "…how do we make it easy for the health professional to give the information in a way that's easy and digestible" – Maria Makrides

Primary health professionals, such as physicians, nurses and midwives, were seen as key stakeholders to engage when developing and implementing guidelines. These health professionals have most interaction with the general public and are seen as trustworthy sources of information and advice. Therefore engaging them to disseminate the recommendations of guidelines and subsequent policy is a key way to actually get people to follow them. The nutrition knowledge of health professionals is variable and they needed training to increase it. Given their trusted position, Maria Makrides was keen to see guideline producers and policy makers enable primary care professionals to give the advice in a digestible way. She suggested that some kind of pack or card with the key messages would be a practical way to help to pass these messages on – especially in time-pressured primary care appointments.

Educate and inform – "…provide the right amount of information to consumers that they can manage with. Too much of it and the consumer will be unable to use it" – Basil Mathioudakis

Educating the public about nutrition was also seen as a key way to facilitate greater engagement with and use of guidelines. This was mainly through incorporating nutrition into the curriculum. Much focus has centred on nutrition labelling, but Furio Brighenti suggests that *"labelling is not enough"* without providing the education to interpret it. When considering nutrition labelling, a consideration is delivering messages in a way that the public can digest (see Box 3).

Box 3: Labelling – how much is too much?

Worldwide there is currently a lot of variation in nutrition labelling, for example the EU has 7 mandatory elements (EC, 2016), and the US is planning for 15 (FDA, 2016). This is an area where setting mandatory requirements should be more evidence-based, Basil Mathioudakis suggests, because these variations in labelling requirements point to an underlying uncertainty about how much information consumers can interpret.

Research funded by the European Union (EU) into the influence of nutrition labelling on food choices indicated that the most promising approach to get consumers reading nutrition information would be to present key nutritional and energy information in a consistent format on the front of packs (EUFIC, 2012). It is easy for consumers to misunderstand nutritional labelling, even from popular systems like front of pack labelling which are considered straightforward. Therefore consistency can help consumers to make informed decisions. However, there is still debate on what information should be presented where (Slavin, 2015). More information is not always better.

The US Food and Drug Administration updated its requirements for nutrition facts boxes on packaged foods in May 2016 (FDA, 2016). These changes were informed by evidence, but also designed to help consumers to understand the information presented to them. For example, making serving sizes clearer, increasing the font size of the calorie contents and including sugars added during manufacture. However, these changes are not without criticism, for example the inclusion of 'added sugars' on nutrition labelling pre-empts the FDA's own research findings and contradicts some consumer research (Slavin, 2015).

Making food-based recommendations – "People are eating foods, they are not eating nutrients" – Arne Astrup

In public-facing guidelines, the trend is towards food-based guidelines designed to deliver the recommended nutritional intake, whereas some previous guidelines have focused on increasing or decreasing particular nutrients. The underlying science and the overall message may still be the same between these two approaches. The nutrient-focused approach advises people to consume a certain amount of a nutrient but leaves them to translate that into foods and then a daily diet. This process can lead to misunderstanding, errors and potentially unhealthy substitutions. US Dietary Guidelines published in 2015 specifically state their move away from recommendations based on dietary components, foods groups and nutrients to recommendations that help people to construct a "healthy eating pattern" that suits them (USDA, 2015). This acknowledges that foods are not eaten in isolation, but rather interact with each other and the individual consuming them.

Food based guidelines should take into account factors that may affect people's choices when choosing foods, such as personal preference, price, convenience and availability. Niv Zmora, PhD candidate at Elinav Lab Immunology Department Weizmann Institute of Science, and Arne Astrup found that diet adherence was improved by providing people with a list of foods to select from to achieve their recommended nutritional intake. This gave participants autonomy and control in choosing which foods they want to eat to construct their healthy diet, based on whichever factors are important to them.

Maria Makrides felt that there was more scope for studying the science of implementation. A lot of effort goes into developing high quality guidelines. Yet the implementation of these is often overlooked and does not have a solid evidence base.

Beware the substitution effect – "So if I don't eat this food or drink this beverage, what do I do as an alternative?" – Furio Brighenti

Another aspect of implementation that must be considered is the substitution effect. If you tell people to eat less of any one food or nutrient, what impact does this have on the rest of their diet? What do they substitute with? There is a potential for unintended harm if people are not given sufficient guidance to inform healthy substitutions. Guideline producers need to bear this in mind when formulating recommendations and policy makers need to consider it when devising policy. For example, advice given in the 1980s to the American public to reduce their fat intake led to greater uptake of 'low fat' products, but overall caloric energy intake has increased over time. So although the percentage of calories obtained from fat has decreased (slightly), this advice did not lead to an overall reduction in caloric consumption (Maki et al., 2014).

Conclusions

- Guideline producers need to consider practical and implementation issues, to ensure that scientifically sound guideline are practically applicable.
- Guideline recommendations and messages need to be delivered clearly to enable all users to understand and implement them.

Nutrition science: similar yet different

During the meeting, where there was a lot of focus on the challenges facing nutrition research and science. However, the perception of nutrition facing unique challenges was refuted by interviewees, who argued that these challenges are not unique, although they may be more pronounced in nutrition research.

Issues included the cost of running high quality studies, compliance/adherence with a given diet or nutritional plan, and length of follow-up required to see if exposure to particular foods has an effect. Dietary components and individual nutrients cannot often be meaningfully isolated to see what the effect of a single food is. This is complicated by the effect of single nutrients being most evident when there is a deficiency, which can be practically and ethically challenging. Also, individual nutrients and foods are consumed in the context of someone's entire diet, for example someone with higher fibre intake may have a generally healthier diet (Maki et al., 2014). Nutrients are also consumed via a range of foods, which then interact in a complex way with the body. Research has to take into account the possible confounding effect of the diet matrix in which food is consumed and individual physiological differences.

The replication of research studies helps to confirm, refine or refute the findings of previous research. It can be a valuable approach when used to confirm observational findings in a randomised controlled trial and many hypotheses have been debunked using this approach (Maki et al., 2014). It is a necessary part of the scientific process but is understandably less exciting and potentially less high profile than new discoveries. Professor Ioannidis felt that the culture within nutrition research of seeking new and innovative findings contributes to the lack of replication in nutrition research. Replication also helps to identify where further research is and isn't required, and – although it may seem contradictory – can prevent waste caused by continually ploughing the same research furrow. Similarly, Holger Schünemann felt that there was a greater need in nutrition research for evidence synthesis – not just in guidelines – to assess the state of the evidence base and where there are gaps that need filling.

Thinking around the problem – "What disturbs me in the field is that there is a background or influence that says "we'll never be able to do these studies"... As long as one says we'll never be able to do them, I guarantee we'll never be able to do them" – Dennis Bier

The main challenge is that it is generally not possible to do randomised controlled trials, the highest form of evidence (although not impossible, see Box 6). Therefore researchers often use observational study methods, reducing confidence in the results and meaning that it is not possible to confirm a causal link. But nutrition researchers should not accept defeat and simply make do with lower quality studies. Firstly, it is challenging but not impossible to do randomised controlled trials and secondly there are some creative ways to perform observational studies to increase their rigour and get a clearer

sense of causation than traditional observational study designs can offer (see Box 4). John Ioannidis has previously declared that a radical rethink of nutrition research is needed – we cannot keep doing what we're doing – and that funding a smaller number of better designed studies that are more likely to provide reliable answers is a potential solution (Ioannidis, 2013, Ioannidis, 2016b).

Box 4: Alternatives to traditional observational study designs

Mendelian randomisation to help determine causation
Mendelian randomisation is a technique for analysing data gathered in observational epidemiological studies. In nutrition, it uses genetic variations that are markers of dietary exposure to infer causality between nutrients and diseases (Marantz, 2010, Qi, 2009, Schatzkin, 2009). It is designed to mitigate the issues of reverse causation and confounding that are implicit in epidemiological studies. Like all methodologies, it is not free from limitations. The genetic associations it studies are based on assumptions and may not be the only factor affecting the outcome observed (Marantz, 2010, Qi, 2009, Schatzkin, 2009). However, it is designed to complement epidemiologic studies and randomised controlled trials.

Nested randomised controlled trials within large cohorts
John Ioannidis advocates nested randomised controlled trials within large cohort studies and biobanks that regularly collect blood samples, as a means of measuring the impact of various lifestyle factors on health outcomes (Ioannidis and Adami, 2008). Such multiple lifestyle factorial experimental (multi-LIFE) designs provide a means of combining the strengths of observational research and randomised controlled trials. Participants in cohort studies or biobanks would be recruited for randomisation to a different lifestyle intervention. Multiple interventions could be tested by using factorial randomisation – randomising people to each intervention in turn. This approach provides opportunities but is not a panacea. There will still be issues around adherence to the lifestyle intervention, participants will not be blinded to the intervention they are following, follow-up and cost of running these trials. However, the potential is that hybridised designs "combine the strengths of both approaches without compounding their limitations" (Ioannidis and Adami, 2008).

How much broccoli did you eat in the last ten years? – "Food exposure and how to assess it properly is one of the major problems" – Furio Brighenti

The first issue in measuring food intake is relying on people to report what they ate during a set period. If done prospectively, for example using food diaries, this can be reasonably accurate but is dependent on people filling out the diary while their recollection is still accurate and honestly reporting their consumption. If retrospectively, this is even more open to potential recall bias. Furio Brighenti considered that this was a weak measure of real exposure and is a major problem for primary research. Even in large-scale, well-conducted studies such as the American National Health and Nutrition Examination Survey (NHANES) there are still issues in the reliability of reporting of nutritional intake. An analysis of nearly 40 years of data NHANES data, found consistent and significant underreporting of caloric energy intake, undermining the reliability and therefore usefulness of this data (Archer et al., 2013).

Niv Zmora reported the opportunity that technology presents to improve the way food consumption is measured in nutrition studies. His experience showed that a smartphone interface for logging food in real time was convenient for participants and researchers – who could analyse data in real time and see emerging trends.

There are some independent and valid nutritional biomarkers that can be used to either triangulate self-report or as an alternative measure of dietary intake and nutritional status (Hedrick, 2012). Currently there are *"excellent predictive biomarkers"* of cardiovascular disease, Luigi Fontana says, but there are none to predict if an individual has a higher risk of developing cancer, dementia or autoimmune diseases – all major causes of ill health globally. Indeed, Dennis Bier bemoaned that there are so *"few [independent biomarkers] given all the nutrients and components of food that we have"*.

Recalled consumption is then matched against food tables to work out someone's nutritional intake, but Professor Bier highlighted that there is great variability in the quantitative nutrient contents of foods – even something as common as a tomato – for example depending on breed, where and when it was grown, and in what soil. He felt that this uncertainty was not always recognised or accounted for in observational studies. Where food products are continually refined and changed, this also presents a challenge to keeping such tables up to date (Maki et al., 2014). In his presentation on the day, Bob Gibson highlighted that food tables are often *"incomplete or out of date"*.

Primary research needs multi-disciplinary teams – "You will never discover the real truth if you don't work together" – Arne Astrup

Just as the perspectives of different stakeholders and professionals are required in guideline development, the same applies to primary studies.

In his studies testing the effectiveness of the New Nordic Diet, Arne Astrup involved a wide range of different people. In designing the diet, he involved chefs from the world famous restaurant Noma to ensure that the recipes were as delicious as they were healthy. Getting famous chefs on board helped create a positive expectation of the diet and this positive association facilitated political buy-in. Then food economists ensured that the diet was affordable and sociologists explored any barriers to uptake that participants were facing. This approach enabled the early identification of potential barriers and continual refinement of the programme to mitigate them. Although involving this range of people makes it more expensive to run these kinds of trials, Professor Astrup felt that it would be a mistake not to. Often these professionals are working on similar, smaller projects in parallel, whereas working together to run larger collaborative trials could be more productive in terms of outcomes achieved and pooling resources can also make financial sense.

Don't demonise industry research – "Right now, the implication is that if it comes out of industry, it is faulty, it's biased, it's perhaps deceptively reported" – Dennis Bier

The vexed issue of industry involvement in research has already been discussed in the context of its impact on potential conflicts of interest in individuals sitting on guideline panels, this is particularly acute in nutrition research because a high proportion of studies are funded by industry.

Industry is an important part of the nutrition research ecosystem. It wants to investigate its products through experimental investigation and nutrition researchers want to find out more about these products. So there is an opportunity to work together in a productive way. The integrity of the scientific methods and the data analysis used in research is not automatically affected by the funding body, unless the relationship between the funders and the researchers is not properly managed.

Dennis Bier suggested that using independent brokers to manage the relationship between funders and researchers could be a potential solution. This would enable a separation of the two, which would help practically with perceptions of conflict of interest and enable those looking at the research to *"focus on the message not the messenger"*, as he put it. This is just one idea and the devil would be in the detail, but it shows that there are potential solutions that can and should be explored. Creative thinking is needed.

Using research funding to steer industry research – "We cannot think that innovation in the food chain is only the responsibility of the food industry" – Furio Brighenti

Industry funds a lot of primary nutrition research because government budgets are limited and it can be difficult for researchers to make the case to government for nutrition research that may have a less obvious and immediate return on investment compared to say cancer drug trials. This means, unsurprisingly, that industry research tends to focus on answering the questions of interest to industry. Furio Brighenti thinks that there is a lot more that governments and policy makers could be doing to engage with industry to steer innovation activities towards mutual interests.

Conclusions

- Nutrition research faces challenges to undertaking high quality primary research, which then impact on guideline production. However, these challenges are not unique to nutrition and there is a lot to be learned from other fields with similar challenges. There are also innovative research methods that can mitigate some of these challenges and could be more widely used than at present.
- As with guidelines, primary research needs to include various professionals who bring different perspectives and insights, to improve the quality and impact of research. This includes industry, whose involvement should not be avoided or demonised, but appropriately managed.

Future innovations and looking forward

The Lorenzini Foundation meeting included some presentations on research, which may have the potential to revolutionise nutrition advice in the future. This led to a lot of discussion about innovation in nutrition science and where the next game-changing innovation will come from. Although everyone was excited by the potential of these innovative research projects, there was agreement that these innovations are still some way off being proven to have a significant impact on human health and changing everyday practice.

Looking ahead, participants agreed that nutrition is important throughout life, but emphasised that nutrition at the start of life is especially important as it is a period of rapid development where any nutritional shortfall can major long lasting effects. Dennis Bier considers the nutritional health of women and girls to be a critical issue for global health, not just the nutrition community, because of its impact on the health of future generations. This echoes the WHO's sustainable development goal focusing on nutrition amongst adolescent girls, pregnant and lactating women (WHO, 2015). So future research and guidelines need to consider early life nutrition as a public health priority.

Personalised nutrition – "…there is logic behind individualising diet according to individual parameters" – Niv Zmora

Personalised recommendations based on individual parameters, rather than broad population based recommendations, were the subject of much discussion. Arne Astrup predicted that in the future global and national level recommendations will be those that are generally good for everybody – or at least do no harm – then personalised data will be used to refine that dietary guidance. The European Union has funded a large-scale project to investigate the opportunities and challenges of 'nutrigenomics', which uses genomic sequencing to personalise nutrition advice (Food4Me, 2011). This project has included randomised controlled trials to explore the scientific potential and qualitative research to understand consumer behaviour and other factors that may affect the translation of the potential of nutrigenomics into reality. Luigi Fontana predicted that his current research into metabolic and molecular factors would lead to *"personalized nutritional interventions that inhibit these pathways"* to prevent or delay disease in individuals.

The speed of innovation in personalised nutrition is such that what would have been science fiction a few years ago is now a reality – albeit in experimental settings and requiring further confirmation. These new scientific discoveries are paving the way for nutrition to become increasingly personalised and precise, which all of the meeting attendees welcomed.

There are steps that can be taken to tailor advice according to some individual parameters. For example the Australian Daily Intake Guide website provides the basic recommended amounts of nutrients that all people should take in (DAA, 2016). However, it has some tailoring according to life

stage (age, pregnant or breastfeeding women), whether people are trying to gain or lose weight, average activity level and size. Although this is quite basic tailoring, it demonstrates that while we wait for personalised nutrition to become a reality in everyday practice (see Box 5), there are intermediate steps that can be taken towards personalisation.

Box 5: The personalised nutrition project

Niv Zmora presented on a personalised nutrition project where people's blood sugar was measured after meals to try to find foods that would prevent spikes in blood sugar. The findings showed how widely people's responses to foods varied, adding weight to the idea that foods are not inherently 'good' or 'bad' but are good or bad for individuals due to their characteristics. This study also found that gut bacteria played an important role in post-meal blood sugar levels. Based on people's gut biota and post-meal blood sugar responses, the researchers were able to tailor the nutrition plan to maintain stable blood sugar levels.

This research indicates the potential for greater personalisation of nutrition and dietary advice, beyond the broad age and gender based population groups currently in use. However, this research is still in an early phase and the findings need to be confirmed in larger studies with longer follow-up (which are on-going currently). For example, people's gut microbiome changes throughout their life and it is as yet unclear how often it would need testing.

This project was oversubscribed, with a waiting list of people who wanted to be involved, and those who did take part were highly engaged with the project. This demonstrates that there is a large demand for personalised nutrition advice. The people involved ranged from those who were very healthy and wanted to add this to the various ways in which they already tried to optimise their health, to those who were currently unhealthy and, frustrated at having tried numerous ways to improve their health, thought that this personalised approach might be more successful.

The gut bacteria tests used in this project would also need to become more widely available and economically viable before they could be used in this way on a larger scale. The speed of innovation means that we may not have to wait long for such tests to become part of the standard battery of tests that primary care physicians use.

Big data – "the biggest opportunity is discovery" – Chirag Patel

Big data has caused a big stir in all areas of life. The idea being – we're collecting so much data about everything now, surely we must be able to put it to some use? Nutrition is no exception.

Chirag Patel, an Assistant Professor at Harvard Medical School, uses computer models to harness the potential of big data in discovering and understanding the complex interactions between different factors affecting health.

He believes that big data analysis can throw up associations not previously hypothesised and can — if done correctly — inform the design of further studies to establish or refute causality. However, there is potential for cherry-picking of associations discovered through multiple post-hoc analyses of existing data sets, which only stop once they find a result and may only report the most "impressive" results (Patel et al., 2016). Distinguishing the *"noise"* of potential associations from the *"signal"* of a probable association can be achieved, says Chirag Patel, through a systematic approach to statistical analysis of big data. In big data, as with other research methods, Professors Ioannidis and Patel both warned that just because something is statistically significant it does not necessarily mean that it is clinically actionable.

The main risk of big data comes when people mispresent or misinterpret associations as causal. Hence it is important to have appropriately skilled and trained people involved, so that they can design appropriate analyses and try to disentangle the *"causal temporal web of nutritional exposures and path to disease"* and understand whether a nutrient is really associated with a disease or merely a *"bystander"* (Chirag Patel).

Guidelines for the next generation – "There's a lot of evidence that we influence the development of the next generation… this is a serious global health issue" – Dennis Bier

Maternal nutrition is an area which shows the power of good research. High quality trials that conclusively showed that folate was an important developmental building block provided the impetus for implementing major public health programmes of supplementation and fortification. Women attend numerous check-ups and appointments during pregnancy, and are motivated to want to improve their health if it will benefit their baby. So, logically, this would be an ideal time to engage them in nutritional education (see Box 6). Maria Makrides felt that this opportunity isn't necessarily being capitalised upon because there is so much other information to communicate – how do you make time to explain about nutrition? She suggests that prioritising a few key nutritional messages may be the solution to this practical problem. This time also provides an excellent opportunity to create new patterns of nutrition and diet that parents can maintain once their child is born, potentially breaking unhealthy cycles to ensure the good nutritional health of the next generation.

Increasingly it is also seen as a good thing for both prospective parents to be in a good nutritional state before they conceive. Professor Makrides points out that there is not much evidence to support this as yet, but that logically it is a good thing and is unlikely to lead to harm.

Box 6: Randomised controlled trials are possible – and here's the proof

As the number of people with food allergies continues to rise globally, there is a lot of debate about when to introduce potentially allergenic foods into the diets of babies. Initially advice was to avoid allergenic foods for the first one to three years of life, but evidence from animal trials and observational studies suggested that avoidance was not an appropriate approach.

Maria Makrides was involved with an RCT that investigated whether introducing egg protein to babies aged 4-6 months affected their chances of developing an egg allergy (Palmer et al., 2016).

The babies were randomly assigned to receive either a powder containing a defined dose of egg protein or a placebo powder that was matched for colour and consistency. A lot of "effort and engineering" was involved in setting up the trial as an RCT, and designing the placebo to ensure the fidelity of blinding. The benefit of this investment is that Maria Makrides feels confident that *"we're going to be able to fully answer the question"*, giving a more definitive answer breaks the endless cycle of 'more research is needed' or 'larger, better designed trials are needed' to confirm the results of studies using methods that provide only indicative findings. Furthermore, using a defined dosage of egg protein enables the implementation of this research as its findings can be easily translated into information provided to families.

Conclusions

- Nutrition advice tailored to individuals is the future of nutrition. There is still a way to go before it is a reality – we need to understand more about the science and the necessary tests are not yet routinely (and affordably) available – but the speed of innovation is encouraging.
- Big data offers great opportunities for nutrition research, in particular to uncover new associations for further examination in clinical trials. It must, however, be analysed responsibly by appropriately trained professionals to ensure that associations are not overstated or misinterpreted.
- Nutrition in early life is crucial; this includes parental nutrition prior to conception and during pregnancy, as well as the quality of nutrition once the child is born. This presents a challenge and opportunity to impact on global public health.

Discussion

The international meeting organised by the Lorenzini Foundation and subsequent discussions with experts, highlighted a number of challenges in nutrition but gave cause for optimism as they offered up just as many solutions.

Nutrition guidelines, like many others, have numerous stakeholders who need to be engaged during the guideline development process. Such engagement has benefits in terms of giving stakeholders a sense of involvement and a stake in the outcome, which can in turn improve the uptake of guidelines. It also brings benefits because it enables guidelines to incorporate the perspectives of these different stakeholders. As we've already explored, in the case of nutrition these stakeholders can include members of the public, sociologists, food economists, policy makers and industry. The involvement of these stakeholders needs to be managed so that their input is provided at the point in the guideline development process where it will add most value. The same is true of primary research in nutrition, where people from outside of the nutrition community can provide valuable perspectives on the design, execution and analysis of research studies. The important message is that the nutrition community needs to include everyone who will make a valuable contribution to their guidelines and primary research.

There are a lot of challenges facing those undertaking primary research in nutrition, which in turn impact on guideline development. It is challenging to undertake high quality primary research, because it is difficult to isolate the effects of individual nutrients or foods and randomised controlled trials – the most reliable study design – are difficult to perform. Therefore nutrition evidence is comprised mainly of observational data, which can tell us about correlation – where two things often coincide and may be linked, but not definitively about causation – whether one of those things causes the other. However, similar challenges are faced by other areas of health so there is no reason to lose hope. This is not to downplay the challenges faced by nutrition researchers and guideline developers, rather to emphasise that there are opportunities to learn from other disciplines who share these challenges. The key is to not lose focus on overcoming challenges, but remain open to new approaches and to creatively think around these challenges.

Involving stakeholders is vital as we have already discussed, but this is not without complications. Conflicts of interest are a major challenge in nutrition – and many other disciplines – affecting guidelines and primary research alike. There is a need for range of people to be involved with research and guideline production to enable the consideration of all relevant perspectives. This includes industry, which has useful and important contributions to make – especially as major funders and producers of nutrition research. The key is managing conflicts by controlling the involvement of potentially conflicted individuals and organisations to ensure that their input is effective and does not skew the findings or conclusions. Conflicts of interest are an issue, but not an unsolvable one.

The limitations of primary research in nutrition impacts on guideline development, in terms of creating uncertainty about the conclusions that can be drawn from the research and in turn the strength of recommendations based on that evidence. Again, these issues are not unique to nutrition. Following international standards to produce high quality guidelines ensures that a systematic and transparent process is followed. Therefore guideline producers can communicate what their recommendations are, how they arrived at them and why this recommendation has been made. It is ok to admit that we don't know for sure yet. The priority is to produce digestible guidelines that clearly communicate the guideline development process so that all users can understand and implement the recommendations. Conversely this may avoid the perception that guideline producers can't make up their minds whether particular nutrients or foods are good or bad.

Nutrition plays a key role in the health of individuals during their lifetime and research into parental nutrition suggests that good nutritional health in one generation can impact on the nutritional health of the next. Therefore it is important that guideline developers throughout the process think about implementation to ensure that scientifically sound guidelines can be fully implemented and impact positively on nutrition. This is primarily achieved through stakeholder engagement during the process to identify and address implementation issues as early as possible in the guideline development or research process. It is also achieved through delivering clear messages that can be understood by all users of guidelines. For example, the trend in public-facing guidelines away from nutrition-based to food-based recommendations that help the general public to compose a diet to try to achieve nutritional intake targets.

Based on these findings we have devised five key ideas for future action, which we believe will help the nutrition field to overcome some of the challenges it faces and to produce better guidelines.

Key ideas for future action

Focus on: including everyone

- All relevant people need to be at the table when formulating guidelines and conducting primary studies to ensure every angle and perspective is considered

Focus on: overcoming challenges

- It is challenging to perform high quality studies in nutrition, but other fields face similar challenges and there are lessons to learn from them
- Open-mindedness and creativity is required to overcome the limitations of observational studies, to take nutrition research forward
- Accurately measuring food exposure is a challenge, technology may help to facilitate ways to collect data in real-time to reduce recall bias
- Keeping up with and being open to innovation is important, but so is being grounded and acknowledging limitations
- Personalised nutrition is the future, in the meantime guidelines should be tailored to groups based on age, gender and physical condition (such as pregnancy)

Focus on: managing conflicts

- Conflicts of interest should be avoided, but can otherwise be managed to mitigate their influence on the guideline process
- Industry can be a powerful ally in conducting primary research and provide useful insights to guideline production, so long as relationships are managed
- Both guidelines and primary research need greater access to sources of funding that will not attempt to exert influence over their direction or findings

Focus on: digestible guidelines

- Nutrition guidelines can and should follow international standards for producing high quality guidelines
- Weak, conditional or qualified recommendations are better than nothing – just explain their limitations
- Uncertainties in the underlying evidence need to be identified and clearly articulated to those using guidelines

Focus on: thinking implementation

- Guidelines have to be implementable – make practical recommendations and beware unintended consequences such as substitution effects
- Guidelines must make sense to all their users – give clear messages in terms people can understand

References

ANDREWS, J. C., SCHUNEMANN, H. J., OXMAN, A. D., POTTIE, K., MEERPOHL, J. J., ALONSO COELLO, P., RIND, D., MONTORI, V. M. & PABLO BRITO, J. 2013. GRADE guidelines: 15. Going from evidence to recommendation - determinants of a recommendation's direction and strength. *Journal of Clinical Epidemiology*, 66, 726-735.

ARCHER, E., HAND, G. A. & BLAIR, S. N. 2013. Validity of U.S. nutritional surveillance: national health and nutrition examination survey caloric energy intake data, 1971-2010. *PLoS One*, 8.

BALSHEM, H., HELFAND, M., SCHUNEMANN, H. J., OXMAN, A. D., KUNZ, R., BROZEK, J., VIST, G. E., FALCK-YTTER, Y., MEERPOHL, J., NORRIS, S. & GUYATT, G. H. 2011. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology*, 64, 401-405.

CUELO-GARCIA, C. A. 2016. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): prebiotics. *World Allergy Organization Journal*, 9, eCollection 2016.

DAA. 2016. *Dietary intake guide* [Online]. Deakin: Dietitians Assosication of Australia. Available: http://daa.asn.au/for-the-public/smart-eating-for-you/nutrition-a-z/daily-intake-guide/.

EC 2016. Food information to consumers - legislation.

EUFIC 2012. Flabel: food labelling to advance better education for life. Brussels: European Food Information Council

FDA. 2016. *Changes to the nutrition facts label* [Online]. Available: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm385663.htm.

FIOCCHI, A. 2010. World Allergy Organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. *World Allergy Organization Journal*, 3, 57-161.

FIOCCHI, A. 2015. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): probiotics. *World Allergy Organization Journal*, 8.

FOOD4ME. 2011. *Food4Me* [Online]. Brussels: European Food Information Council Available: http://www.food4me.org/ [Accessed 01/09/2016.

GRADE. 2016. *GRADE* [Online]. GRADE working group. Available: http://www.gradeworkinggroup.org/.

HEDRICK, V. E. 2012. Dietary biomarkers: advances, limitations and future directions.

IOANNIDIS, J. P. A. 2013. Implausible results in human nutrition research. *BMJ*, 347.

IOANNIDIS, J. P. A. 2016a. Commentary: salt and the assault of opinion on evidence. *International Journal of Epidemiology*, 45, 264–265.

IOANNIDIS, J. P. A. 2016b. We need more randomized trials in nutrition - preferably large, long-term, and with negative results. *American Journal of Clinical Nutrition*, 103, 1385-1386

IOANNIDIS, J. P. A. & ADAMI, H.-O. 2008. Nested randomized trials in large cohorts and biobanks: studying the health effects of lifestyle factors. *Epidemiology*, 19, 75-82.

MAKI, K. C., SLAVIN, J. L., RAINS, T. M. & KRIS-ETHERTON, P. M. 2014. Limitations of observational evidence: implications for evidence-based dietary recommendations. *Advances in nutrition*, 5, 7-15.

MARANTZ, P.R 2010. Rethinking dietary guidelines. Critical Reviews in Food Science and Nutrition. 2010 Dec; 50 (s1), 17-18.

OXMAN, A. D., LEWIS, J. N. & FRETHEIM, A. 2007. Use of evidence in WHO recommendations. *Lancet*, 369, 1883-1889.

PALMER, D. J., SULLIVAN, T. R., GOLD, M. S., PRESCOTT, S. L. & MAKRIDES, M. 2016. Randomized controlled trial of early regular egg intake to prevent egg allergy. *Journal of Allergy and Clinical Immunology*.

PATEL, C. J., BURFORD, B. & IOANNIDIS, J. P. A. 2016. Assessment of vibration of effects due to model specification can demonstrate the instability of observational associations. *Journal of Clinical Epidemiology*, 68, 1046-1058.

QI, L. 2009. Mendelian randomization in nutritional epidemiology. *Nutrition Reviews*, 67, 439-450.

SCHATZKIN, A. 2009. Mendelian randomization: how it can - and cannot - help confirm causal relations between nutrition and cancer. *Cancer Prevention Research*, 104-113.

SLAVIN, J. L. 2015. The challenges of nutrition policymaking. *Nutrition Journal*, 14.

THOMPSON, D. F. 1993. Understanding financial conflicts of interest. *New England Journal of Medicine*, 329, 573-576.

USDA. 2015. *Dietary guidelines for Americans 2015-2020: eight edition* [Online]. United States Department of Agriculture. Available: http://www.cnpp.usda.gov/dietary-guidelines.

WHO. 2003. Food based dietary guidelines in the WHO European Region. Copenhagen: World Health Organization Europe.

WHO. 2015. *Goal 2: end hunger, achieve food security and improved nutrition and promote sustainable agriculture* [Online]. Geneva: World Health Organization. Available: https://sustainabledevelopment.un.org/?menu=1300#.

WHO. 2016a. Addressing and managing conflict of interest in the planning and delivery of nutrition programmes at country level: report of a technical consultation convened in Geneva, Switzerland, on 8-9 October 2015. Geneva: World Health Organization.

WHO. 2016b. *Obesity and overweight* [Online]. Geneva: World Health Organization. Available: http://www.who.int/mediacentre/factsheets/fs311/en/.

YEPES-NUÑEZ, J. J. 2016. World Allergy Organization-McMaster University guidelines for allergic disease prevention (GLAD-P): vitamin D. *World Allergy Organization Journal*, 9.

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