

Workshop Report

Nutrition economics – characterising the economic and health impact of nutrition

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Abstract

There is a new merging of health economics and nutrition disciplines to assess the impact of diet on health and disease prevention and to characterise the health and economic aspects of specific changes in nutritional behaviour and nutrition recommendations. A rationale exists for developing the field of nutrition economics which could offer a better understanding of both nutrition, in the context of having a significant influence on health outcomes, and economics, in order to estimate the absolute and relative monetary impact of health measures. For this purpose, an expert meeting assessed questions aimed at clarifying the scope and identifying the key issues that should be taken into consideration in developing nutrition economics as a discipline that could potentially address important questions. We propose a first multidisciplinary outline for understanding the principles and particular characteristics of this emerging field. We summarise here the concepts and the observations of workshop participants and propose a basic setting for nutrition economics and health outcomes research as a novel discipline to support nutrition, health economics and health policy development in an evidence and health-benefit-based manner.

Key words: Nutrition economics: Cost analyses: Cost-effectiveness: Functional foods: Health economics: Health outcomes

The important role of food and nutrition in public health is being increasingly recognised as crucial for its potential impact on health-related quality of life (HRQoL) and economics, both at the societal and individual levels. Increasing epidemiological and scientific evidence demonstrates clear links between food and health maintenance/disease

development⁽¹⁾. In developing countries, morbidity and mortality are directly related to protein and energy malnutrition, while in many Western countries, health officials have begun to actively promote the consumption of healthy foods while reducing the amount of energy in the diet. In parallel, the food industry has proceeded to

Abbreviations: HRQoL, health-related quality of life; QALY, quality-adjusted life years; RCT, randomised controlled trial.

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tackle nutrition- and health-associated challenges in two complementary ways: (i) by removing or replacing unhealthy ingredients (based on both national and international recommendations) such as *trans* lipids, salt and added sugar; (ii) by incorporating healthy or health-promoting ingredients and bio-active compounds in new products, for example vitamins, *n-3* fats, plant extracts, fibres, flavonoids, probiotics and prebiotics. Scarcity cannot be eliminated while health spending is presently rising faster than GDP in most of the developed countries⁽²⁾. The question of how to optimise the use of scarce resources, and the linkage between nutrition, health and welfare should be studied in a broader and more scientific way. This should include aspects and methodologies that compare nutrition-related costs and health outcomes, in order to sustain value-based decisions within systems providing health care. A favourable impact of food on nutrition-related disorders and general health status may have a positive impact on health care expenditure, thus contributing to public health and the sustainability of health systems in general. Meanwhile, the joint development of a discipline like nutrition economics may help the policymakers to encourage individual responsibility for a healthy lifestyle.

The context of nutrition economics

Over the last decades, the interest in evidence-based health care has grown considerably. In about the same time period, the economic evaluation of health care technologies has been instituted. The introduction and development of this discipline was a response to the demands of decision makers who, faced by the increasing pressure on the health care budget, ask for information not only on the efficacy and costs but also on the cost-effectiveness of healthcare treatments. The principles of economic evaluation have now become well established. Such evaluations analyse the costs, savings and health effects of a health technology, as compared to an alternative (constituting a part of what has been named as Health Technology Assessment). Therefore, health economics is as much about health outcomes as it is about money. Until now, no systematic and specific approach has been developed for the assessment of the impact of food products on health, and HRQoL in our society. A methodology specifically suited to the area of nutrition is lacking, despite a clear need and important requirement from policymakers as well as a direct interest for consumers. According to a recent World Bank report on health-enhancing foods: 'Currently, cost-effectiveness of functional foods in reducing disease burden and lost productivity is an important research gap'⁽³⁾. In a similar manner, a report by the European Commission states: '... there is virtually no information on the cost-effectiveness of functional food, i.e. it is unclear at what cost the expected health benefits come. Studies indicate that functional food may help

prevent diseases that currently impose a heavy drain on health care budgets'⁽⁴⁾.

To fully appreciate the context of nutrition economics, it is necessary to be aware of the specific characteristics of food. Food is, in the first place, the source of macro- and micronutrients for humans. However, the complexity of food and its interactions with multiple interdependent genetic, physiological, metabolic and psychological processes that have an impact on human physical functioning and psycho-social well-being requires a holistic approach, different from the pharmaceutical field, typically targeted to specific functions. Food products have to be distinguished from classical pharmacological treatments. To assess the health and economic impact of food products and nutrition, it is not sufficient to apply the methods of pharmacoeconomics without modifications. Pharmacoeconomics was initially developed to allow health authorities to decide on an efficient allocation of available resources between alternative strategies or treatments (pharmaceuticals) and as an aid for decisions in health care priority setting. Other features that limit a straightforward use of pharmacoeconomic models in the area of nutrition include: (i) differences in the evaluation of risk between pharmaceuticals and food products – in clinical drug evaluations, risks to some patients are traded-off against benefits to the group, whereas in food regulation, known risks are, in principle, not acceptable; (ii) prevention and risk reduction *v.* treatment also challenge the economical assessment – food is for everybody, whether healthy or diseased, while medications are restricted to a relatively small number of subjects; (iii) food products have their nutritional profile and form a part of the global diet, adjusted to local nutrition recommendations; (iv) the choice of a food product is made by the consumer and therefore the choice is based on multifactorial decision making being more random or influenced by habits, preferences and perceived benefits, unlike a medically prescribed product; (v) some food products are only available through specialised channels (e.g. food for special medical purposes), but most of them are sold in shops and supermarkets without any advice except for advertising; (vi) as a rule, food products are not subject to reimbursement by social security or welfare programmes (although certain refund experiences of specific products by health care systems or insurance companies have been tried). The link between the consumption of a food product and future health status is more difficult to establish than the effect of a drug treatment. To match the above-mentioned specificities of the health-enhancing food sector, the goal would be to generate methodologies in order to correctly predict the impact of food-related health effects and health economic outcomes from a broader perspective.

Outline of a multidisciplinary expert workshop

A workshop was organised to gather specialists from different disciplines. The agenda of this expert workshop was introduced by an overview of the basics in health economics for the nutrition specialists and a presentation of clinical issues related to nutrition for the health economic and health outcomes research experts. The panel discussion was guided by statements drafted from existing guidelines for health economics^(5–9) to provide the basis of establishing nutrition economics as a new discipline. A set of articles focusing on the economic aspects of nutrition was provided to give the participants some further background information^(10–18). For the subsequent debate on the methodological issues, it was important to determine what the term food or nutrition covers.

The following categories were distinguished: (i) conventional food: all basic food in the daily diet; (ii) functional food: similar in appearance to conventional food, consumed as part of a usual diet and which has demonstrated physiological benefits and/or reduces risk of chronic disease beyond basic nutrition; (iii) infant formula and infant foods: food specially made for meeting the nutritional requirements of infants during breastfeeding period or children up to the age of 3 years; (iv) food for special medical purposes⁽¹⁹⁾.

It was decided that the main focus of the discussions would be on functional foods, partly for practical reasons and because functional foods suggest a beneficial effect in the general population addressing a risk factor for future morbidity. Study protocols for nutritional intervention trials are designed according to the predefined benefits and/or risks that can be influenced by functional food as shown by measurable parameters. This also applies to conventional food that has shown a beneficial effect (functionality) on a target population in a nutritional intervention trial setting; dietary fibre or fatty acids can be a functional food, as well as products that have undergone substitution of an ingredient, e.g. replacing saturated by polyunsaturated fat, and that can play an important role in health outcomes and possess economic sequelae. Target groups of functional foods within the general population can be identified as healthy or non-diseased populations with risk factors or, to put differently, diseased populations that have not been diagnosed yet. The outcomes of existing nutritional intervention trials provide a concrete framework as a starting point for testing the potential relevance for conducting an economic analysis. The specialists participating in the meeting evaluated the issues that are relevant when exploring the field of nutrition economics, and the details of their conclusions are presented below.

Target audience of nutrition economic studies

Clear overlap exists between pharmacoeconomics and nutrition economics, and several aspects of these areas are relevant to similar target audiences. However, one distinguishing group is specific for pharmacoeconomics: those who absorb or bear the costs – in health economics, these are commonly referred to as the payers and represent the entity that will be in charge of at least some of the medical expenses for diseased people. This category does not have its equivalent in nutrition economics. Another differentiating feature is the reimbursement of medical treatment *v.* an individual choice of food purchase that consumers pay for themselves. The healthy population without treatment also contributes in supporting the burden of the national health care expenses. Nutrition economics will thus be relevant not only for the health care providers and policymakers, but also for the general public.

Physicians are another important target audience. The physician or health professional will mostly be interested in the clinical effectiveness rather than in the costs. In addition, without any regulatory framework, a practitioner may be reluctant to recommend directly to anyone the use of a particular food product for health on the grounds of personal liability. Recommendations or guidelines endorsed by a scientific or professional society, regulatory body or health care providing system are required; but at this stage, evidence to support those recommendations is for the most part lacking. There is a need for a trustworthy source to guide health care professionals in applying combined health and economic outcomes of nutrition in their daily medical practice. Professional organisations responsible for guidelines may therefore be another target audience. For example, if there is a recommendation from the American Heart Association, physicians will have a solid ground to follow that guidance. Considering the increasing pressure on health care budgets, physicians may well be willing to provide nutritional advice that is cost-effective or even that contributes to net cost-savings (either immediate or in the future). In addition, a reduction of their workload may be a result. Within hospitals, the interest of health care providers is more oriented towards budget impact data and data related to hospital stays than towards cost-effectiveness data and even less towards food-related cost-effectiveness. Employers may form another target audience for nutrition economics because of the potential to avoid future productivity losses. Data on the impact of nutrition-related health conditions on productivity losses, in terms of either absenteeism or presenteeism^(12,20) (i.e. reduced productivity while at work despite illness) are emerging.

Nutrition-related disorders cause an increasing need for health care interventions and also may have a considerable impact on HRQoL, including physical functioning and psycho-social well-being⁽²¹⁾. Therefore, the targets

that have been identified are numerous: advisory bodies (e.g. National Institute for Clinical Excellence in the UK, German Institute for Quality and Efficiency in Health Care in Germany, College voor zorgverzekeringen in the Netherlands, TLV (Dental and Pharmaceutical Benefits Agency) in Sweden, Health Technology Assessment Agencies and Units members of International Network of Agencies for Health Technology Assessment, European network for Health Technology Assessment and EuroScan, Health Technology Assessment International), central public policymakers (e.g. National Health Service in the UK and Haute Autorité de Santé in France), regional public policymakers, third-party payers, care-providing institutions (e.g. hospitals and nursing homes), health care professionals, individual consumers, employers and even food producers (e.g. food companies and farmers) when planning investments for future development.

Conclusion. A reduction in the health and economic burden achieved or avoided through food will be of interest for many different stakeholders, including healthy individuals who contribute in financing the health care needs.

Perspective of nutrition economic analyses

In health economics, an economic evaluation is conducted from a defined perspective which determines the costs and benefits that are taken into account. It relates much to the discussion on the target audience. In the field of nutrition policy, all costs and effects are important regardless who is paying for, or receiving, them, to ensure a true societal perspective. Individual purchases of food products are made by consumers using their own money. They will benefit from well-conducted studies on benefits, but will judge value for money themselves through the price and perceived benefit. In this situation, the focus shifts from cost-effectiveness towards willingness to pay. Thus, the economics of nutrition can be much broader or narrower than cost-effectiveness analysis as applied to pharmaceuticals. In England and Wales, the National Institute for Clinical Excellence is already evaluating public health programmes (for example, exercise-promoting programmes or tobacco-reduction programmes⁽²²⁾ which are much broader than product-related approaches) using a cost perspective that includes the whole public sector and not just health care. Agencies in other countries such as Australia and Canada are also going down that particular route. In the Netherlands and Germany, the general taxpaying public is showing increasing interest in preventive health care. One of the driving elements of health policy at the moment is to persuade people to take responsibility for their own health and achieve maximal benefits with the health system spending minimal money on it. This puts the question of perspective in a context that bridges the gap between the needs of the health care system and the interests of the non-diseased individuals who are bearing part of the costs, whether financial or in

another way, and who have to be convinced of changing their lifestyle⁽²³⁾.

Different interesting scientific issues arise depending on the adopted perspective. It comes back to the attribution of costs to different people. Nutrition economic analyses may provide valuable evidence of food habits likely to reduce part of the burden of health care. The general public who already accept personal expenses for their own well-being and fitness might be more receptive to positive messages rather than being warned constantly on the dangers of fat, salt and sugar.

Conclusion. The perspective of nutrition economics needs to be broader than that usually applied in cost-effectiveness analysis in health care.

Outcome measurement

The measurement of health outcomes in nutrition depends on the user group and is related to the specific nature of food as well as to specific aspects concerning preventive treatment in sub-healthy consumers. This leads to additional methodological issues. It is not easy to achieve measurements of the global effects of food habits within the general population. There is a problem of proof related to the choice of endpoints that is difficult to handle. Some interventions have more immediate effects than others. Hence, a couple of questions arise: How to measure the preventive effect, if it is produced several years later?^(24–26) What will be the right moment to start monitoring? Will it be possible to work with health, rather than with disease markers, and if so what would be their nature? For example, in osteoporosis, bone density is a sensitive surrogate marker, but this does not easily permit the demonstration of the superiority of a specific diet (in a nutritional intervention trial) on the target population of seniors. The most convincing evidence would come from studying 25 year olds, or even children over time and relating the intakes early on to their bone health observed later in life. However, the effects seen would not only be associated to aspects of the diet like the Ca level but also to a multitude of other factors that would need to be considered. This would take much time and financial resource. The food industry potentially has not enough resources to engage in such programmes and it will not be a priority for policymakers who are more likely to focus on expensive treatment regimens to induce a rapid budget impact. Which pathway can we expect for the methodological approach in the field of nutrition economics? There is a three-point continuum on which this can be based: efficacy, effectiveness and efficiency (Fig. 1). Efficacy is concerned with answering the question ‘does it work?’ in a clinical trial setting. Effectiveness refers to ‘does it work under real daily life circumstances?’ and efficiency adds cost considerations to the latter by asking ‘is it worth it?’ Along this continuum, the evaluation of nutrition-related health benefits

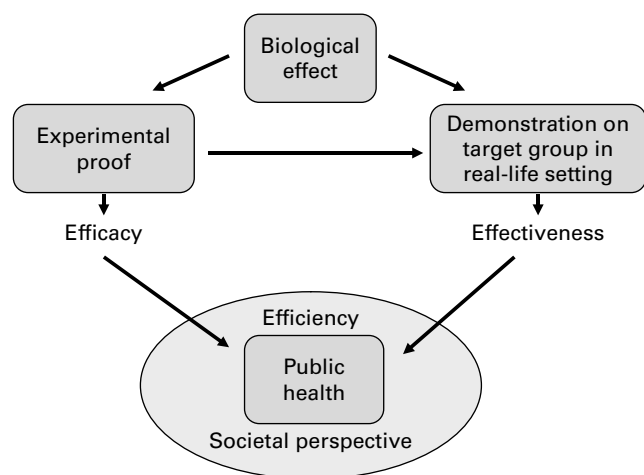


Fig. 1. Three-point continuum of nutrition economics.

represents an essential part of the cost-effectiveness pathway. Adapted study designs will be needed and may include observational, experimental and pragmatic trials using registries. A registry is an observational study, having a much larger sample size than a randomised controlled trial (RCT) and more comprehensive data collection⁽²⁷⁾. People are followed prospectively and data are collected on clinical outcomes reported by clinicians, as well as on resource use, functional status and HRQoL as reported by the subject. Observational studies are fully naturalistic and they have, in spite of concerns on internal validity, a high external validity. The use of a registry suits perfectly with the concept of evidence-based medicine, which means that clinical encounters should be supported by scientific conclusions based on sound data as much as possible. The large size of a registry is appropriate for health economic evaluation in food and, although the effort should not be underestimated, allows the development of statistically solid multiple regression equations for adjustment of confounding variables, which can be incorporated in a health economic model. Furthermore, an improvement of information systems in health care would make large-scale and long-term studies more feasible at a reasonable cost and although people are very slow to pick this up, this is gradually starting to happen⁽²⁸⁾. Long-term outcomes are usually not interesting for payers, but they are relevant in health economic analyses from the societal perspective. It now becomes possible to do pragmatic trials with automated data collection through linked primary and secondary care data systems.

Conclusion. Outcome measures are similar to those considered in preventive interventions and protocols should include observational and experimental designs depending on the nature of the outcome to be measured.

Cost-effectiveness analyses

Economic evaluations express the relation between a measured benefit and the cost of the intervention that is needed to obtain this benefit. In a medical setting, the cost items that are directly associated to the intervention are more or less easy to determine; indirect cost and long-term costs consequences of a chronic disease state or of its avoidance are more difficult to include and will often be based on estimations. In medicine, the most obvious benefit will be cure, but many other possibilities exist, such as effects on morbidity (e.g. reduced stroke rate and higher response rates). In the field of nutrition, there can be a variety of measurable health benefits such as a decrease of symptoms, a risk reduction or health maintenance, a delayed onset of disease development and even increased longevity. The identified health gain needs to be quantified or valued in order to establish the impact of a given intervention or programme on the health status of the concerned target population. In health economics, this value is commonly derived from the HRQoL and expressed in quality-adjusted life years (QALY). Today, one of the most commonly used final outcomes of a cost-effectiveness analysis is being calculated as the additional costs per QALY gained. However, one may question whether the QALY is perfectly suitable to capture the outcomes of nutrition.

The methods of economic analysis routinely used in the pharmaceutical sector were developed from academic studies in the 1960s and 1970s. The methods were used by policymakers in national health systems, such as the National Health Service in the UK, and in the 1980s, the pharmaceutical industry began to use cost-effectiveness analysis to communicate the benefits of their products⁽²⁹⁾. The most rapid increase in the use of cost-effectiveness analysis came when it became a requirement of the reimbursement authorities in many countries, beginning with Australia in 1992.

Although in some countries the reimbursement agencies work with an explicit cost per QALY threshold as an aid in decision making, many other countries are reluctant to use an explicit cost-effectiveness threshold. So far, the food industry does in general not include items on cost and utility data in their nutritional intervention trials, mostly designed to demonstrate a cause-effect relationship. HRQoL from the subject's direct viewpoint is a relevant criterion. The main difficulty lies in assessing the changes in quality of life in a (sub) healthy person, looking for protection against a long-term disease risk. Nutrition-related risk reduction is often an add-on to a normal lifestyle in healthy persons with a potential health problem. In other cases, there can be significant quality of life benefits in a relatively short period of time; for example, when obese people start to realise that they can do things they could not do before, beginning to feel better about themselves and becoming less sedentary. So,

in a programme targeted at people who have a pre-existing problem, HRQoL impact might be easier to appraise, depending on the availability of validated nutrition-specific measurement instruments. In any case, specific ways of measuring HRQoL in sub-healthy people are needed. It will be necessary to identify, measure and value in some detail the impact of an intervention on the subject's functioning and well-being.

A frequently used approach to adapt cost-effectiveness from a trial to a real-life situation is modelling. Modelling studies may also provide the necessary cost-effectiveness information using various existing data sources for clinical and economic information. Modelling studies are based on decision analysis, which is a well-recognised method for analysing the consequences of decisions that are made under uncertainty⁽³⁰⁾. Projections about food's effectiveness and expected costs can be modelled using realistic and explicit assumptions based on data from clinical studies. In addition, modelling often helps overcome the practical limitations of prospective studies, particularly for preventive programmes that may require longer-term extrapolations of health effects and cost implications. If diet is considered as a key component of health, it might be worthwhile to see if nutrition plays an enabling or hindering role in adopting or in reinforcing a healthy lifestyle.

Conclusion. For determining benefits in nutrition economics, the appropriateness of the available quality of life questionnaires for answering the research question at hand should be checked. Development of nutrition-specific measurement instruments suited to the complexity of the field might be needed.

Comparisons in nutrition economic assessment

In health economics, the use of comparators is mandatory and often a comparison is made with 'standard care' or 'usual care'. A placebo is only to be used when no better alternative is available. The pharmaceutical trial world has moved on from true placebo control to active treatment comparators, due to ethical issues. In nutrition studies, the results are very much dependent on how the placebo or comparator has been designed. This is nicely illustrated when looking at lactose intolerance: whatever you chose as a placebo, a subjective overestimation of the frequency of milk intolerance may considerably affect the study outcomes^(31–34). The key question then is what is the best comparator? Should a probiotic yoghurt be compared to a placebo yoghurt? What is a placebo yoghurt? Is it an acidified milk product without bacteria or is it fermented milk with or without active starter cultures or active metabolites? If the study design implies that the control group will have to consume a product that is not part of their daily diet, this induces an interference that might invalidate the outcomes of the experiment. Depending on what you want to investigate, no intervention can also be an acceptable comparator. Linked to the need for identifying the right comparator,

it might be important to identify upfront what is the unmet need and what might be the real outcomes on health. There are not many nutrition studies that have actually compared competing products; if a new dairy product is added to the diet, people will not eat it on top of their usual quantity of food, and they might stop eating some other food product. It has to be defined how such changes in diet can be taken into account in the evaluation.

Conclusion. Comparisons should be carefully defined and controlled; design and analysis are important issues to address.

Time horizon

Health maintenance, health improvement and disease risk reduction are among the most important benefits of nutrition in the sub-healthy population. There are usually no short-term measurable benefits and benefits will not immediately show cost savings and gains in QALY. In chronic conditions, delayed onset of disease and secondary prevention constitute valuable information that can be modelled when valid data are available. This refers to the earlier discussion about evidence-based medicine and science driving the whole continuum. Many RCT do make it clear what the eventual long-term effects are. In all cases, it is important to have a clear sight on positive effects as well as on the negative ones that should be monitored and reported. Some effects that can be evidenced by identified markers on a shorter term can already be linked to long-term outcomes. An example is evidence of the clinical benefit of the phytosterols, where the reduction of LDL-cholesterol is linked to a reduction in long-term clinical events, which is generally accepted in the medical community. A future impact may offer an appealing argument for health policymakers and it can be one of the factors for nutrition economic modelling. For nutrition evaluation, the time horizon is by definition long term and although it seems attractive to use the QALY as an outcome measure, this technique may not be perfectly suited in its present form to measure the outcomes of food products. Of note, in the care sector, there are also discussions going on presently relating to the question of whether the QALY can be used as a sufficiently comprehensive measure of benefit⁽³⁵⁾. One of the challenges for the field of nutrition economics will be to develop methodologies adapted to the complexity of nutritional research and the interactions between diet, lifestyle and multiple other factors. It should be kept in mind that measurement of the long-term impact of diet and food habits will be relevant for all nutrition-related disorders, whether it occurs through reducing risk factors or is due to improvement of under-nutrition or overeating.

Conclusion. There is a challenge to develop methodologies adapted to the complexity of nutritional research and the interactions between diet, lifestyle and multiple other factors. Modelling potentially plays a very prominent

role in nutrition economics as the benefits in many cases will take long time spans to develop.

Identification of costs

Looking at the impact of nutrition benefits on the public sector budget is timely and it will need to be broadened out in order to address it from a true societal perspective. This means that all related costs and involved resources should be quantified, no matter who pays for them. Typically, in economic evaluations of health care interventions, a distinction is made between direct and indirect costs, and between costs incurred inside and outside the health care sector⁽³⁶⁾. These data may be collected through several sources and, depending on the study population and the health condition concerned, the cost categories that may be important include prescription and over-the-counter medications, consultations with the general practitioner, visits to the outpatient department, out-of-pocket costs for alternative ‘therapies’, costs of productivity losses, cost of informal care giving, savings associated with delayed entry into a residential home and cost of accompanying services looking after children or the elderly. In the case of a health benefit induced by a functional food product, the price difference of this product as compared with the traditional food item has to be taken into account when conducting an economic evaluation. Thus, there is a complexity in identifying the costs due to the huge number of variables that may enter in the analysis and by the way in which they will be quantified.

Conclusion. The costs to be taken into account should consist of not only direct but also indirect costs in order to produce a comprehensive picture of the resources involved.

Discounting

In health economic analyses, the principle of discounting is important. It aims to translate the value of future costs and health effects in today’s rate. This is done because costs and effects may occur at different points in time and people have a so-called positive time preference, which means that they like to have pleasant things as soon as possible, rather than in the uncertain future, while they would rather postpone unpleasant things and costs. A high discount rate or a far ahead benefit will lead to a lower present value of the analysis results. Therefore, discounting is in general not in favour of preventive programmes, as for example vaccination^(37,38). Experiments seem to indicate, as would be expected, that if you offer individuals a set of options, some of which include themselves sharing in the benefit and some do not, the discount rates obtained in the former are much lower than the discount rates in the latter^(39,40). People are concerned with the balance of their own benefits over their lifetime and this is what conditions their willingness to pay. Can there be an argument in nutrition

assessment technologies of using discounting rates that are different from the rates that are commonly used for pharmaceutical cost-effectiveness analyses? In the long-term context, one should be aware that due to discounting, the future cost savings and gain in QALY can be reduced substantially. Considering a different discount for preventive programmes will not be accepted by the health economic community, because it is in conflict with general economic principles of valuing the future benefits.

Conclusion. It is too early to establish a recommendation about discounting in relation to the long-term impact of nutritional health effects.

Internal and external validity

How should generalisability of results in a nutrition economic analysis be evaluated? Internal and external validities have to be addressed separately. Internal validity is the extent to which the analytic inference derived from the study sample is correct for the target population. External validity is the extent to which the economic analysis performed in the study sample is also true in the external population.

The assessment of nutrition benefits was discussed in detail, and the group expressed the following viewpoint on the quality of the evidence on efficacy. On the one hand, RCT have a high internal validity and are considered the gold standard for proving a functional benefit, as well as the cause–effect relationship. However, data from RCT do have in general a low external validity because they have strict inclusion and exclusion criteria and treatments are protocol driven⁽⁴¹⁾, leading to overestimation of units of health care utilisation. Although randomisation is usually applied to balance the confounding variables, inclusion criteria of patients and selection of investigators are fairly rigid. Of course, health economic data (effectiveness and resource utilisation) may be collected alongside a RCT^(42–45). However, this is not always ethical or feasible. For example, in a comparison of nutrition with drugs, randomisation can be performed, but adequate blinding will be complex or even impossible in some cases.

For external validity, when it comes to nutrition economics, the design has to reflect the real-world setting and pragmatic trials will allow avoiding or reducing the problem of missing evidence. Depending on the type of food and its beneficial effect, it is acceptable for the health economic experts to require the highest possible evidence. For example, observational studies may provide adequate evidence, depending on the endpoint. Experimental trials are seldom performed for a public health intervention, because people would be in part extracted from the conditions where the intervention is going to be used afterwards. Even in RCT, the biomarkers are not always tied to diseases in ways that are meaningful. Of course, this raises the question of the quality of trials. In the pharmaceutical world, there is a perception that

a pragmatic trial is less rigorous. In fact, this is not always the case; it is possible to conduct a pragmatic trial with good design principles, leading to adequate levels of evidence. For example, the first guidelines for CVD management were based on the Framingham Study⁽⁴⁶⁾. The conclusions come from a series of cohort studies and still remain part of the evidence that now relies on a mixture of observational and interventional data. So, pragmatic trial that is well done is not bad evidence, rather it is evidence of a different type.

Conclusion. Causal relationships have to be demonstrated in randomised clinical trials but complementary informative data collection from the real-life setting is needed for health economic decision making.

Dealing with uncertainty

The two blocks of traditional uncertainty to standard health economic evaluations are first of all associated to the fact that the missing link between short-term surrogate endpoints and the long-term hard outcome is usually not established through a RCT, but can be based on observational cohort studies or case-control studies. Since the real-life setting in nutrition economics increases the number of confounding factors, more extensive sensitivity analyses will be required. Secondly, uncertainty is more than only variance in a distribution of input parameters and is also related to the choice and type of data sources used in the extrapolation. The issue of uncertainty can be further managed through scenario analyses based on the modification of the underlying assumptions or data sources of the model. Other studies can subsequently be used to validate the outcomes of the model. There are many interactions between variables, which indicates that nothing short of a probabilistic sensitivity analysis would be adequate, because it is not possible to change one variable at a time without having modified several of the others. In some cases, it will be possible to have very clean trial designs, for example when adding an antioxidant to juice, but the majority of the questions are more complicated. If you want to change the level of a particular variable, it will presumably have a knock-on effect on many other factors. One could take the extreme example of elderly people in a nursing home, quite often suffering from constipation. If you intervene against constipation, it will actually improve appetite. The increased food intake increases their well-being and activity level and then many more elements have been modified than just the one product that has been given initially. This difficulty even holds when considering the balance between benefit and risk. This can easily be illustrated by the following examples. Acetaldehyde is classified as a carcinogen. But it is also normally present in fruit, vegetables, yogurt and in infant foods, and is a common metabolic intermediate product in human physiology. In many food products, the presence of acetaldehyde seems to be associated

with other protective components which may counteract its detrimental effects. However, in alcohol products, it can rapidly lead to problems. What is the best way to take this into account when conducting nutrition intervention studies and how should the information obtained be translated to both the public and health professionals as well as to regulatory bodies? We know that sulphites in red wine are harmful to health. But again, moderate wine consumption or other alcohol-containing drinks is also associated with some health benefits⁽⁴⁷⁾; and people will also factor in their own personal taste, the pleasure they get from the substances they appreciate when eating or drinking them. Will there ever be a way to produce any transparent quantitative analysis for the benefits and risks, the real balance between the negative and the positive? The right people to make a decision would be those subjects themselves, who are taking the risks and getting the benefits. But this requires awareness and understanding of the available information. A way to get over this problem is the use of consumer-based self-reported outcomes, which are based on full knowledge of the intake and the use of validated HRQoL measures, with standardised administration guidelines to minimise the measurement error.

Conclusion. Uncertainty will be one of the big challenges in the field of nutrition economics.

Conclusion

Taken together, it appears important to define the new area of 'nutrition economics' carefully as the discipline dedicated to researching and characterising health and economic outcomes in nutrition for the benefit of society. Early involvement of all relevant parties in defining the principles, proof of concept and the link between evidence-based medicine and nutrition economics will be mandatory for managing the complexity and for warranting a solid foundation in developing this new field. In general, prevention and public intervention programmes carry an upfront cost before potentially bringing the health care expenses down. The question is whether the health benefits are large enough to justify the additional costs regardless of who has to pay for them. The nutrition economics approach aims at answering this question through outcome measurements that reach specific quality objectives. It will be important to conduct economic analyses for the different target audiences, to put costs in perspective, to calculate cost savings and health benefits and to quantify them in a manner that takes into account the complexity of the question. The specific outcomes of interest should be assessed in a real-life routine situation, not in a controlled experiment, as is the case for preventive measures and programmes. In the case of cost impacts from nutritional benefits, the possibility of a dominant result in terms of net cost-savings cannot be excluded and a specific nutrition economic model certainly will be useful to obtain

information about what might be expected. Scientists with a multidisciplinary approach to nutrition and economics will be essential for generating the required information that spans the whole cycle. Also, food companies may play a decisive role in their ability to influence the penetration rate of cost-effective health-enhancing products. On a European level, there are several interesting programmes demonstrating how to involve decision makers in comparable multi-disciplinary processes. A forum such as created by Health Technology Assessment specialists, including decision makers, scientists, regulators, industry and international organisations, driven by nutritional scientists, would have the potential to be quite productive and facilitate the implementation of nutrition economics as a kind of policy platform. Examples of similar approaches can be found in the recently established 'Policy Forum' by Health Technology Assessment International (<http://www.htai.org>). There are a number of allied disciplines from which knowledge and modelling experience can be drawn for developing and improving our knowledge in the field of nutrition economics. To better comprehend nutritional sequelae, the group of experts participating in this workshop suggest initiating an interest group bringing together nutrition researchers and specialists interested in policy to become engaged as an independent entity on establishing an economic agenda, in addition to a scientific research agenda.

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