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Title: Health Economics and Nutrition: A Review of Published Evidence

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Abstract: The relationship between nutrition and health-economic outcomes is important at both the individual and societal levels. Not only do nutritional choices made by individuals affect their health condition, thus influencing productivity and economic contribution to society, but also nutrition interventions carried out by the state have the potential to affect economic output in significant ways. This paper reviews studies of nutrition interventions where health-related economic implications of the intervention have been addressed. Results of the search strategy have been categorized into three areas: economic studies of micronutrient deficiencies and malnutrition; economic studies of dietary improvements; and economic studies of functional foods. It is found that although a significant number of studies have calculated the health-economic impacts of nutrition interventions, approaches and methodologies are sometimes *ad hoc* in nature and vary widely in quality. Development of an encompassing economic framework to evaluate costs and benefits from such interventions is a potentially fruitful area for future research.

Key Words: nutrition economics, malnutrition, micronutrient deficiencies, dietary improvements, functional foods

INTRODUCTION

The relationship between nutrition and health is well documented and associations between various nutrient impacts and nutritional interventions have been widely reported. The addition or removal of specific components into or from an individual's diet can result in significant health improvements with the potential to result in non-trivial economic benefits. There is growing interest in the economics of nutrition, which broadly can be thought of as the process of researching and characterising health and economic outcomes following nutrition interventions and nutrition recommendations for the benefit of society.[1] Assessing the health and economic impact of food consumption patterns or specific changes in nutritional behaviour on health and disease is highly relevant, for a number of reasons. For example, such assessments have the potential to play an important role in the development of nutrition recommendations and could also inform regulatory processes related to nutrition labelling and health claims.[1]

One way in which the efficacy of a nutrition intervention can be evaluated is by examining the changes in costs and outcomes it causes. This could include measures of utility, reflecting the preference that an individual (or society as a whole) might have for a particular health state. It has been shown that when faced with a choice regarding a specific change in nutrition, if a rational individual stands to gain more in utility than the disutility associated with their personal cost of making the change, they are expected to choose a course of action that maximizes their expected utility.[2] The consequences of individual nutrition choices can then be aggregated to determine the impact on populations. A variety of metrics exist for measuring the health-economic impacts of nutrition at the macro level, including changes in the direct costs of treating health conditions that could be improved with nutrition interventions; improvements in productivity resulting from decreases in morbidity and premature mortality; generalized monetized estimates of adjusted life years; and condition-specific willingness to pay (WTP) estimates of gains in utility from improved health states.

A nutrition intervention can be evaluated at the macroeconomic level in terms of potential gains and losses to society as both indirect and societal costs. When the total costs of a nutrition intervention are less than the prospective benefits, there is a potential gain in societal welfare from the intervention. Such potential welfare gains do not require every single member of society to benefit; rather, they require only that the total potential gains outweigh the total potential losses. However, on a personal basis, a quantifiable benefit or incentive must be foreseen to make a change in nutrition behaviour attractive. The typical methods used to evaluate these types of potential welfare gains at the micro-level include cost-minimisation analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA). It is critical that the value of an intervention, as well as the costs, be known in order to calculate whether a net benefit exists.[3] One study discussed methods for evaluating the economic benefits associated with improved health resulting from changes in diet and exercise [4]; other work has endeavoured to link the microeconomic aspects of health economics with the welfare related macro aspects by developing a welfare-theoretic model predicated upon the individual utility function.[5] An exploration of the health economics of preventative nutrition, outlining the economic burden of numerous nutrition-related health problems, has also been carried out.[6] This review will identify existing research which characterizes health and economic outcomes in nutrition for the benefit of society.

Given increasing pressure on health care budgets, the development of food and functional food products along with nutritional therapeutic modalities is facing new challenges. The assessment of the value-for-money of nutrition interventions should be a common goal for regulatory authorities, public health policy makers and the scientific community. To date little research has been undertaken with respect to identifying the economic aspects associated with nutrition interventions or programs and their health benefits.[7] The objective of this review paper is therefore to conduct a systematic review of the existing literature to properly contextualize the current state of the field, with the hope that improved understanding of relevant methods and findings will facilitate the development of an encompassing evaluation framework with the flexibility to be applicable to a wide array of interventions.

METHODS

A multidisciplinary expert workshop was held to elucidate the scope of the relationship between nutrition and health while identifying key issues that should be considered when proposing new studies of the economic consequences of nutrition interventions and policies.[1] During that workshop, a subset of the current evaluation methods used in health economics and pharmacoeconomics was reported to be not completely suitable for the evaluation of the socioeconomic impact of nutritional habits in general, and of specific nutrition interventions in particular. At that workshop the term “nutrition economics” was coined to refer to a specific sub-field within health economics, highlighting the need to identify existing studies in order to facilitate the further development of adapted methodologies. With the findings of this workshop in mind, a strategy for a comprehensive systematic literature review was formulated.

Search Strategy

The databases in Table 1 were queried with the search strategies and critical assessment as specified. The initial key words were defined based on the thesaurus of the databases being searched by a skilled information specialist; biomedical databases were queried for economic and nutritional terms and economic databases were queried for nutrition terms. Figure 1 provides a flowchart summarizing the search process. It should be noted that searches for specific nutrients were not undertaken; although this is acknowledged as a factor that has the potential to limit the scope of this review, it is believed that the search strategy employed did reveal the preponderance of literature given that studies on specific nutrients were likely to be detected by using broad nutritional terms.

Targeted attempts to search out "grey" literature beyond the documents contained in the databases named in Table 1 were made with Google Scholar, a tool which uses Google to search the internet for peer-reviewed papers, theses, books and articles from academic publishers, societies, preprint repositories, universities and other scholarly organizations. *Scirus,* a tool which searches MEDLINE citations, ScienceDirect ejournal articles, patents, technical reports and scholarly web pages, was also used in attempt to find "grey" literature, as was the AgEcon Search database. A significant body of research was found to exist in the "grey" literature for economic studies on micronutrient interventions. This literature, largely comprised of reports from various non-governmental organizations (NGOs), was not included in the present report because it was of varying quality, for instance containing non systematic reviews or epidemiological studies of small populations, and was in many cases out of date compared to the published scientific literature. Nevertheless, "grey" literature with a focus on other economic nutrition relationships was included if it met the inclusion criteria.

Inclusion and exclusion criteria according to Patients Intervention Comparison Outcomes (PICO) Question

Titles and abstracts of the studies returned by the search were reviewed independently by two researchers against the following inclusion and exclusion criteria:

Patients – since nutrition interventions have the capacity to benefit wide cross-sections of the population, all studies done on human subjects were considered for inclusion. Studies carried out on animals or those that attempted to extrapolate from animal subjects were excluded.

Intervention – all studies concerning a change in diet (either the addition of a healthy substance or the removal of unhealthy substance) were eligible for inclusion. Studies on nutrition interventions where the effect (efficacy or effectiveness) had not been established before, either through randomized controlled trials (RCTs), observational comparative studies (cohort or case-control) or at least pre/post observational studies, were not included. Studies dealing with enteral nutrition were not considered, as this is a special nutrition application in hospital surroundings and often under medical supervision or during medical procedure, rather than a food pattern or change in diet. Also, studies in which the treatment was a medical product or otherwise not considered food were not included.

Comparison – economic research often relies on simulation models or "natural experiments." As a result, relevant comparisons can include a simulated or observed section of the population which has not received a nutrition intervention or is receiving a different type of treatment, or historical comparisons in which economic parameters before or after an intervention are evaluated.

Outcome – studies reporting a quantifiable change in health outcomes, which may result in changes to the direct or indirect costs associated with the change in health status due to the nutrition intervention, were included. Studies in which other measurable economic parameters related to nutrition, and relevant to the socio-economic environment, were calculated also merited consideration for inclusion. Studies not involving any economic aspect of health outcomes from a nutrition intervention were excluded. The references and citations of all relevant articles were cross-checked for additional relevant studies with only English-language written studies being reviewed.

A special mention of how studies of obesity, a complex medical condition which can be affected by nutrition as well as by other lifestyle and environmental factors, were addressed within this review may be necessary. Obesity management interventions were included if there was a clear food-related nutritional component to the intervention as well as measurement of an identifiable health outcome. For example, a change in body mass index

(BMI) or body weight is likely to reduce the risk factor for a number of chronic diseases; however, if the link to a related health disease such as diabetes or coronary heart disease was not established in the paper, then the study was not included. Though the economics of obesity is an important and interesting topic, a complete investigation of it would be beyond the scope of this review, and related research has already been reviewed elsewhere.[8]

A final issue with respect to methodology pertains to how this review approaches evaluations of major nutrition programs. The United States Department of Agriculture (USDA) has a number of large and important nutrition programs including the WIC (Women, Infants and Children) and SNAP (Special Nutrition Assistance Program, formerly the food stamp program). These programs are important and a considerable number of evaluations of their general efficacy along with economic efficiency have been conducted. However, the USDA itself urges extreme caution in interpreting conclusions from studies of these programs for a variety of reasons.[9] Accordingly, such studies were not included in this review.

RESULTS

The initial search of the databases listed in Table 1 resulted in over 13,000 returns. Many of the returns were excluded because their focus was not upon human nutrition or because they were editorial comments not consisting of attempts to quantify the health-economic effects of a nutrition intervention. A preliminary review of search findings suggested categorization of the literature into three areas: 1) research examining the economics of food fortification and dietary change to improve micronutrient intake and malnutrition; 2) research relating to economic improvements as a result of healthier diets; and 3) research aimed at studying the economic aspects of foods which can provide a health benefit beyond normal nutrition, referring mainly to functional foods. A discussion of studies falling into each of these three areas is found in the following sections.

1) Economic Studies of Micronutrient Deficiencies and Malnutrition

Studies examining various economic aspects of micronutrient deficiencies and malnutrition are summarized in Table 2. Twenty-six studies were included; seven were cost-effectiveness analyses, two were cost-benefit analyses and two were RCTs; others varied from simulation models to systematic reviews of RCTs. As Table 2 shows, micronutrient deficiencies in the low and middle income world are the most commonly studied areas with respect to economic studies of nutrition interventions. While these deficiencies can have tremendous economic costs, their treatment, specifically through improving the nutrient content of food, has been demonstrated to be very cost effective. Studies included in this section comprise the existing research on the economic consequences of food improvements devised to correct micronutrient deficiencies including fortification of staple foods with vitamin A[10-13] iron,[13-18] iodine,[13,19] zinc[18], and folate[20-23], as well as polices aimed at increasing consumption of foods naturally high in these minerals.

To date the most comprehensive study pertaining to the economics of micronutrient food interventions identified the feasibility and cost-effectiveness of 122 food fortification strategies in 48 countries.[24] Addressing the criticism that the cost estimates of previous studies are out of date, not sufficiently detailed, and lack rigour, the authors estimate the CEA of micronutrient fortified foods in those countries building upon an existing model.[25] Notable in that paper is the detailed and transparent description of the methods used in cost-effectiveness calculations. The results of their analysis are reported in the cost per disability adjusted life year (DALY) saved, which provides a single index whereby the morbidity and mortality to a particular disease can be measured. For micronutrient interventions, the cost per DALY saved is considered to be the best available method to quantify the economic benefits of the intervention.[25,26] Folate (also known as vitamin B_9 or folic acid, a nutrient essential for human development) deficiency is notable in that it has also afflicted the populations of developed countries. Folate deficiencies often result in neural tube defects (NTD), which occur at a very early stage of development; increased consumption of folate during pregnancy can reduce the risk for NTD. The cost effectiveness of folate fortification has been studied extensively.[20-23] An interesting aspect of the economic consequences of NTDs is the difficulty associated with measuring adverse health consequences that occur very early in life—a large part of the economic benefit of folate fortifications is the increased future productivity of newborns who do not become afflicted by a NTD. Since the assumptions around future earnings and the discount rate can influence these results significantly, appropriate estimation methods should be used.

A relatively new strategy for dealing with micronutrient deficiencies is biofortification, a method of breeding plants resulting in their being naturally high in micronutrients. The benefit-cost ratio for investments in plant breeding for crops designed to reduce anaemia has been found to be high.[27] A few authors have considered the economic underpinnings of biofortification[28,29]; one particular study calculated found high levels of cost-effectiveness for rice bio-fortified with Vitamin A.[30] In general, when a food is fortified or biofortified with micronutrients it has a lower cost structure than would an equivalent but separate supplementation program. Economic studies of biofortification applications in countries including India, Australia, New Zealand, and Uganda have been carried out.[30-34] Another method of adding micronutrients to food is through genetic modification of a crop in such a manner that the edible portion of the harvested grain is high in a specific micronutrient by design. The economics of both genetically enhanced micronutrient rich rice and mustard have both been studied.[26,35,36] These programs are, for the most part, the same in that the portion of the population receiving the micronutrient enhanced food should become healthier, potentially leading to a valuable economic benefit. Researchers carried out a study of home fortification with zinc in Pakistan and found that a reduction in diarrhoea and improvement in haemoglobin concentrations led to a reduction in child mortality, higher earnings and increased IQ scores.[37]

The literature on improving basic nutrition by alleviating protein and energy malnutrition (PEM) is somewhat limited. Correcting PEM in the developing world has the potential to improve a number of health conditions which can have a considerable economic impact. Some research has shown that PEM can play a major role in susceptibility to infectious diseases such as HIV/AIDS, tuberculosis, and malaria.[38] The Copenhagen Consensus, a panel of eminent economists, ranked nutrition investments 2nd, 5th, 11th, and 12th among their recommendations to advance global welfare. The economic elements of malnutrition and associated manifestations could prove to be an interesting endeavour for future research.

2) Economic Studies of Dietary Improvements

Once the basic needs of human nutrition have been met by addressing core nutrients and mineral and micronutrient deficiencies, focus can be shifted to dealing with improving human health as part of a normal diet. Increasing consumption of nutrient-dense food or reducing consumption of unhealthy foods in the diet can lead to improvements in health, especially with respect to many chronic health conditions. Scientific research increasingly confirms that human diet can have a significant impact on disease, quality of life (QOL), and healthy longevity. Detrimental dietary patterns such as high intake of fat/saturated fat and low intake of calcium and fibre-containing foods such as whole grains, vegetables, and fruits can cause conditions that impair the quality of life and accelerate mortality. Diseases and health conditions identified as being good candidates for preventative nutrition strategies include: age-related macular degeneration (AMD), certain birth defects, cataracts, colon cancer, coronary heart disease (CHD), diabetes, hypertension, kidney stones, low birth weight, obesity, osteoporosis, pre-eclampsia, and stroke.[39]

The review identified thirty studies relating to quantifiable health and economic benefits from dietary improvements (Table 3). While few assessments have been made to estimate the economic cost of poor or unbalanced diet, it has been conservatively estimated to be over $70 billion annually in the United States.[40] This implies that if dietary improvements were made by all or a portion of the population, then a portion of these costs could be saved, resulting in an economic benefit to both public and private interests. One of the first attempts to put an economic value on nutrition interventions estimated the effect of reducing saturated fat on the incidence and cost of CHD in the United States.[41] A key finding of this research was that a relatively small reduction in dietary saturated fat could result in annual savings of almost $13 billion. Another well-studied relationship in nutrition is the relationship between sodium and CHD; one study found that a 3g per day dietary salt reduction could result in $10 to $24 billion in health care savings.[42] Other research into dietary reductions of calorie consumption in the American diet also showed that modest dietary changes could result in billions of dollars in savings in health care costs.[43,44] Showing that the economic benefit of dietary improvement is not limited to the developed world, it has also been found that a voluntary reduction in salt intake is a cost effective method of reducing chronic disease in a number of low and middle income countries. Other research examined the effectiveness of two strategies to reduce sodium consumption, and found that a mean population reduction in sodium intake of 9.5% would lead to considerable reductions in both morbidity and disease costs.[45,46]

McCarron and Heaney examined the healthcare savings related to consumption of adequate dairy products and estimated savings from a reduction in obesity, hypertension, type 2 diabetes, osteoporosis, kidney stones, certain outcomes of pregnancy, and some cancers to be in excess of $200 billion over a 5 year period.[47] Osteoporosis, characterized by reduced bone mineral density, has the potential to be improved by increased consumption of calcium and vitamin D. While research demonstrating the cost-effectiveness of supplements as a treatment for osteoporosis has been reported,[6] it is surprising that similar studies were not found for food fortifications or dietary changes to improve calcium and/or vitamin D intake during the course of this review.

Obesity, a serious health condition seemingly at the opposite end of the spectrum from the problem of malnutrition, is often seen in the less wealthy population. Studies have demonstrated that obesity carries significant economic costs, estimating that the cost of obesity in the United States is $99 billion and that the future cost of obesity in China will climb to nearly 9% of their gross national product by 2025.[48,49] A health technology assessment reviewed the cost-effectiveness of pharmaceutical and surgical interventions and conducted a Markov simulation to the cost-effectiveness of a low-fat diet combined with exercise in an obese population, finding a relatively high cost per QALY gained.[50] However, the only disease reduction conceded was diabetes, making this particular estimate very conservative. Policy decisions such as “junk” food taxes and food labelling requirements designed to increase consumption of healthy foods and decrease the consumption of unhealthy foods are another method with the potential to improve public health and as a result reduce health care costs. Recent work modelled the impact of tax and incentive polices aimed at increasing fruit and vegetable consumption in France, finding that some strategies were cost-effective in increasing healthy food consumption while reducing the risk of death from cancer and CHD.[51] Another study examined four potential food taxation-subsidy alternatives and found that all would be regressive from an economic standpoint; moreover the economic burden of such taxes would be more harsh for the poor than for the rich. Nevertheless, the authors found that a combination of taxes with subsidization of healthy foods would produce overall population health gains.[52] Similar research explored the potential effects of applying the UK’s value-added tax to a broader range of foods, finding that the incidence of ischaemic heart disease would decrease. However, consumers would have to spend more on food, implying that their incomes should be raised to compensate.[53] This would be particularly true for those in lower income groups. A subsequent paper calculated the impacts from health, nutrition and economic perspectives of related measures in the UK, and concluded that such policies, while having the potential to improve health outcomes, could have the undesirable effect of actually reducing consumption of healthy foods.[54] As an alternative to such "fat tax" policies, one study investigated the health and economic impacts of "thin subsidies" designed to encourage increased consumption of fruits and vegetables, and found that the cost per life saved of such a policy compared favourably to other existing programs in the US.[55]

The potential savings resulting from the US's *Nutrition Labelling and Education Act* were calculated and it was determined that the expected subsequent reduction in body weight in some sections of the population could result in $63 to $166 billion, a saving greater than the cost of implementing the act.[56] Further research found that limiting "junk" food marketing to children would be an extremely cost effective intervention tool for government.[57] Governments also generally possess the ability to institute outright bans on consumptions of certain food types if there is a net benefit to doing so; one study concluded that the reduction in healthcare costs from banning trans fats in Canada would more than offset the food industry cost increases that the ban would cause.[58] In general, most policy and educational efforts to improve health through nutrition have shown to be cost effective. Population wide policy interventions are likely to offer excellent value for money in the prevention of obesity through the health nutrition impact of improved labelling and a "junk" food tax.[59]

There has been some research with respect to the potential role of education initiatives in generating positive nutrition outcomes; for example, Rajgopal et al examined the costs and benefits of the expanded food and nutrition education program run by the cooperative extension serve at Virginia Tech University.[60] They found that participation in six to twelve nutrition education lessons could result in healthcare savings due to the delay and/or avoidance of poor nutrition related chronic diseases. Similar results were found in Oregon,[61] Iowa,[62] and New York.[63]The cost effectiveness of child nutrition education efforts in Peru has been studied; however, that research did not have a defined health benefit and did not meet the inclusion criteria for this review. The authors found that a targeted education program was cost-effective in reducing stunting and mortality.[64] The cost-effectiveness of different "minimal contact" educational strategies to reduce serum cholesterol was assessed; it was found that short counselling sessions could be cost-effective in reducing cholesterol.[65]

The so-called "Mediterranean diet" provides an intriguing example of a cost effective approach in reducing the cost of CHD at a micro level.[66,67] However, defining Mediterranean diet in detail is difficult and interpretation of the published information depends on this. The Mediterranean diet involves eating primarily plant-based foods, such as fruits and vegetables, whole grains, legumes and nuts; replacing butter with healthy fats such as olive oil and canola oil; using herbs and spices to flavour foods; limiting red meat; and increasing fish and poultry consumption. Though the Mediterranean diet holds promise for improving the health of its consumers, food availability could limit its widespread adoption. Two studies have examined similar dietary modifications involving increased consumption of fruit and vegetables, which are believed to reduce the incidence of some types of cancer and, as a result, yield cost savings.[68,69]

The cost effectiveness of a number of nutrition interventions including the Mediterranean diet, intensive lifestyle change, a reduced fat diet, various nutritional counselling strategies, and extensive educational efforts have been examined,[11] and it was found that all ten of the nutritional interventions investigated were cost effective. It was also noted that nutrition intervention can constitute a highly efficient component of a strategy to reduce the burden of disease. An ongoing research project is focusing on examining the economic and health impacts of the *Programme for Complementary Food in Older People in Chile*.[70] This program aims to increase the health and economic situation of the specified group, and is notable as a proactive approach in addressing changes in the demographic characteristics of the population using nutrition as a tool to deal with the economic and health demands of an aging society. A study of blood serum cholesterol reduction resulting from the implementation of Swedish guidelines for non-pharmalogical treatment of hypercholesterolaemia found that both low-and-medium intensity strategies reduced cholesterol by only a small amount; per-subject treatment costs were five times higher in the medium-intensity group.[71]

It may be reasonable to conclude that interventions aimed at positive dietary changes are cost-effective through a reduction in the burden of chronic diseases which can be prevented through healthier nutrition, as well as production losses avoided through a healthier workforce. The economic benefits of encouraging and educating the public on improving food habits will be a profitable aid for policymakers dealing with the increasing health- and economic burden of healthcare.

3) Economic Studies of Functional Foods

Little research has focused on researching and characterizing the health and economic outcomes of functional foods; as a result the search revealed only seven studies (Table 4). Two were cost-effectiveness studies, two were cost of illness analyses, and three were other heterogeneous studies. There is a natural evolution from pursuing adequate nutrition via increasing micronutrient consumption using food as a means to improve health beyond basic nutrition. Food scientists and nutrition researchers are continuously devising new functional foods, loosely defined as food products designed to provide health benefits beyond basic nutrition. Consumption of these foods has the potential to improve human health; in turn this health improvement has the potential to provide economic benefits.

The earliest example of an economic benefit arising from the use of a functional food was a study of the cost-effectiveness of grain fortified with cyanocobalamin and folic acid.[72] Folic acid is normally considered a vitamin; however, the benefit focused upon in the study was a lowering of plasma homocysteine levels for the prevention of CHD. This goes beyond basic nutrition, making the fortified grain in this study more of a functional food. The authors found this particular fortification could be cost-effective and have a major benefit on populations' health for primary and secondary prevention of CHD, but noted that further research may be required to confirm that homocysteine-lowering therapy decreases CHD event rates.

Research on the relationship between cholesterol and CHD has led to a number of studies focusing on the ability of functional foods to lower serum cholesterol and hence reduce the incidence and costs of CHD. Plant sterol and stanol addition in foods, which have been shown to inhibit cholesterol absorption, have been studied particularly extensively. The cost-effectiveness of plant sterol and stanol enriched margarines and dairy products has been demonstrated as efficient in reducing cholesterol and CHD related costs.[73,74] A recent study found that significant healthcare savings should result from introduction of plant sterol enriched functional foods to the Canadian market.[75]

Additional research on the economic benefits of functional foods with the potential to reduce the incidence of CHD includes an examination of the economic benefit of trans-fat free canola oil. Research found that such a product would result in significant economic benefits to Canadian society.[76] Other research employed a simulation model to calculate the cost effectiveness of omega-3 fatty acids in the reduction of CHD and found supplementation would result in fewer fatal myocardial infractions and was cost-effective in treating CHD.[77] An important aspect of omega-3 fatty acids not covered by that study was the ancillary health benefits such as the prevention of cancer and other neurological diseases; further research is needed to fill this gap.

Flax is considered by many to be a functional food ingredient because it is rich in alpha-linolenic acid (ALA), an omega-3 fatty acid. Because of this property, flax consumption has the potential to reduce the incidence of diseases such as CHD, diabetes, cancer, kidney disease, and Alzheimer's disease. The reduction in healthcare costs that could result from increased flax consumption in Canada has been estimated to be between one and three billion dollars annually.[78]

It is noteworthy that clinical research and limited economic analysis indicate the potential for functional foods to be cost effective across a more diversified area of health concerns; some examples include antioxidants and eye disease[79]; cancer and omega-3 fatty acids and antioxidants[80,81]; Alzheimer's disease and omega-3 fatty acids[68]; conjugated linoleic acid and obesity; probiotic/prebiotics and bowel diseases and diarrhea[82-84]; and prevention of atopic dermatitis.[85-88]As these new technologies spread, the challenge will be to develop new methodologies to analyse and quantify the long time frames and complex nutrition health relationships associated with these functional foods. Because new functional food products are being developed continuously, it is important to ensure that economic analyses of the impacts of these interventions are carried out using appropriate methodologies.

DISCUSSION

Micronutrient interventions provide a useful illustration of how a nutritional change can result in health and economic outcomes with societal benefits. The efficacy and effectiveness of increased micronutrient consumption in alleviating micronutrient deficiencies is well established, while the economic benefits of improved micronutrient intake have been studied extensively in high, low and middle income countries. As a public health tool, micronutrient fortifications are often cited as one of the most cost-effective means of quickly improving a targeted population's QOL. While much of the research has focused on low and middle income countries, the tools, methods, and lessons are broadly applicable. The possibility of analysing the cost-effectiveness potential of micronutrient interventions should be fully explored.

The relationship between diet and economic activity is complicated and evidence of causality runs in both directions. When people are adequately nourished they are in better health and more productive, and as people become wealthier they can afford to eat better and their health improves. The relationship between improved nutrition and a country's national income has been studied in some low and middle income countries. While the basic malnutrition is an important public health concern in the low and middle income world, to date much of the economic research related to malnutrition has focused on micronutrient deficiencies, sometimes referred to as the hidden hunger. Humans require small doses of a number of different micronutrients in order to maintain normal bodily function. Though it is possible to obtain an adequate dose from a healthy diet, in some situations, especially in low and middle income countries, proper micronutrient nutrition is not always possible. As a result, micronutrient deficiencies affect a significant portion of the population, with associated adverse health effects ranging from blindness to severe birth defects. The costs of treating these deficiencies as well as the productivity lost due to micronutrient deficiency related morbidity and mortality have been found in various studies to be economically significant, and interventions aimed at correcting micronutrient deficiencies have generally proved to be cost effective. Micronutrient interventions provide a compelling example of an area in which nutrition improvements benefit society from an economic perspective.

In developed countries, a change in unbalanced or detrimental food habits can result in substantial health care cost savings. Numerous factors not related to nutrition, including genetic and lifestyle issues influence obese subjects' ability to lose excess weight and overweight and obesity can only partially be alleviated by adapted nutrition. The potential benefits of healthier food habits and dietary improvements might have a higher impact in preventing weight gain and maintenance of a correct body mass index. In general, findings of this literature review indicate that dietary improvements can result in substantial health care cost savings. This should be reflected in nutrition recommendations and nutrition counselling as an added value to health benefits on both individual and target population levels.

The functional food market is growing rapidly. The potential for significant savings across a wide range of diseases illustrate the largely untapped potential of functional foods to reduce the incidence of nutrition-related chronic diseases and healthcare costs. Coronary heart disease is a leading cause of death and a significant health concern in the developed world. As such, it is not surprising that the majority of the functional food studies detected in this search were related to functional foods designed to reduce the risk of CHD. From an economic analysis standpoint, the tools and biomarkers are very similar to methods used in pharmaco-economic evaluations of statin-type pharmaceuticals. Although this makes an economic analysis modelling of CHD reducing functional foods relatively easy for economic researchers, a substantial number of differences exist between developing economic evaluation models of pharmaceuticals versus functional foods. These differences are related mainly to the need for different approaches to measure effectiveness. While it is clear that in the case of drugs RCTs are the standard, in the case of nutrition, population-based, properly conducted observational studies should be the focus. In fact, effectiveness of the interventions on real life basis is extremely important because many context dependent factors could influence the final outcomes of these interventions. Further investigation of the costs of such approaches is needed, but this will be challenging because of the confounding factors and long timelines associated with analyzing a number of nutrition-related diseases. This makes a complete analysis complex. Though small in number, studies available to date suggest that functional foods are cost-effective and can be powerful tools to reduce illness and the associated costs.

A limitation to this work is that the literature search and interpretation focused primarily on the economic side of the “value for money” equation rather than on the health-related quality of life (HRQOL) value outcome side. A critical review of the effectiveness outcomes (including HRQOL) can be an important consideration but was beyond the scope of the present paper. It should also be noted that the term “cost-effective” has been used in a number of studies cited in this review as a proxy for cost saving. In reality, cost effectiveness is not solely about cost “savings”, but can in fact involve increasing expenditures. This is the case when the added value (e.g. improved QOL) of a nutrition intervention can be demonstrated to offset the additional costs.

CONCLUSION

The range of studies presented demonstrate that from the most basic level of providing adequate nutrition, to simply improving normal diets by the addition of healthy food or the removal of unhealthy foods, or through the introduction of functional foods which are designed to provide a health benefit beyond normal levels, nutrition can be a powerful force in improving both the health and economic status of society. Much of the work to date has been *ad hoc* with economic analyses based largely on the particular subject area and without an overarching, well-defined framework. Future research would benefit from the development of such a model since it would allow for a uniform and complete measurement of the economic costs and benefits borne by all stakeholders. With increasing pressure on healthcare budgets across the world, the potential to cost-effectively “demedicalize” health care costs with nutrition should be fully examined as opportunities present themselves. The fact that many of the interventions described in this review, which have proved to be cost effective, have not yet been implemented implies that policymakers and the public need better information on the economic potential of nutrition-related health effects. In summary, further development of the methods for economic evaluations of nutrition interventions and promoting their use to inform public policy decision makers should be considered priorities in setting future research direction.

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Table 1 **Databases consulted, systematic literature review**

Database Name	Major Focus	Records Content (see notes)	Key Words	Results
EconLit General	Economics	1,013,000 b, j, t, v, w	Nutrition, Economics	2,190
RePEc/IDEAS	General Economics	865,000 b, c, j, w, o	Nutrition, Economics	461
AgEcon Search	Applied Economics	unknown a, j, w	Nutrition	3,175
NHS-EED	Health Economics	24,000 a	Nutrition	333
DARE	Health Interventions	15,000 r	Nutrition, Economics	2
HEED	Health Economics	41,000 b, j, v, w	Nutrition	485
HTA	Health Technology Assessments	8000 s	Nutrition	32
EURONHEED*	Health Economics	unknown l, s	Nutrition	206
CEA registry	Cost of Effectiveness	2,000 s	Nutrition	17
CODECS	Econ. Evaluations	820 s	Nutrition	7
PEDE	Econ. Evaluations	2,000 s	Nutrition	70
PubMed/MEDLINE	Biomedical	19,000,000 j	Nutrition, Economics, Cost, Benefit	6,232
PAIS	Public Affairs	480,000 b, j, r, s, v	Nutrition, Economics	83

a denotes abstracts, b denotes books, c denotes chapters, j denotes journal articles, l denotes bibliography,
o denotes software, r denotes reviews, s denotes study, t denotes theses/dissertations, v denotes collective
volumes, w denotes working papers * denotes discontinued

Table 2 **Economic studies of micronutrient deficiencies and malnutrition**					
Reference	Population	Study Design	Intervention/comparison	Outcome(s) measured	Economic findings
Popkin et al. (1980)[10]	General	Benefit cost analysis	Vitamin A education; fortification; supplementation	Mortality, blindness, morbidity, treatment costs	Benefit cost ratios showed fortification (between 2.4:1 and 8.4:1 depending on populations and assumptions) and mass dosage capsule programs (between 5.8:1 and 21.0:1) had benefits much greater than costs
Phillips et al. (1996)[11]	Women of child-bearing age & young children	Secondary data from donors & NGOs	National sugar fortification program; targeted capsules distribution program; promotion of home food production combined with nutrition education	Number of high-risk person years of vitamin A deficiency eliminated	Cost per high-risk person achieving adequate vitamin A was US $0.98 through fortification; $1.68-1.86 through capsule distribution; $3.10-4.16 through food production/education
Loevinsohn et al. (1997)[12]	Children 6-59 months in the Phillipines	Various sources: government & UN documents; RCTs; others	Universal application of supplements vs. broad targeting vs. narrow targeting	Cost effectiveness of reducing child mortality	First year avg. cost: universal approach $67.21/death averted; broad targeting $144.12/death averted; narrow targeting $257.20/death averted
Horton (2008)[13]	General population	Economic calculations	Four aspects of undernutrition: protein-energy malnutrition and deficiencies of iodine, iron, and vitamin A	Economic losses	Cost effectiveness of nutrition interventions found to be very high
Sari et al. (2001)[14]	Children 4-6 years in Indonesia	Double blind placebo controlled intervention study	Iron fortification (1 mg elemental Fe/g every week for 12 weeks) vs. no fortification	Hemoglobin concentration; anemia prevalence; serum ferratin concentration	Per-capita cost of supplement was US $0.96-$1.20 for the 12 weeks of intervention; may be an affordable method for

					combating iron deficiency in low-to-middle income group children
Horton et al. (2003)[15]	General population in 10 low and middle income countries	Economic calculations using assumptions based on previous studies	Iron fortification vs. no fortification	Benefit to cost ratio for long-term iron fortification programs	Median benefit to cost ratio of 6:1 for the 10 countries; 36:1 if discounted future benefits to cognitive improvements are included
Hunt (2002)[16]	General population in India and Bangladesh	Economic calculations using assumptions based on previous studies	Investments in biofortification for rice and wheat vs. no biofortification	Benefit to cost analysis for biofortification	Benefit to cost ratios between 19.3:1 and 84.7:1 and total (agricultural plus nutrition) net benefits between $2.837 billion and $7.988 billion depending on assumptions regarding variety adoption rate & anemia reduction rate
Baltussen et al. (2004)[17]	Women 30-44 and perinatal infants in four regions (South America, Africa, Europe, Southeast Asia)	Population model	Iron fortification or iron supplementation vs. no fortification or supplementation	Maternal mortality and perinatal mortality	Iron supplementation would avert <12,500 DALYs in European subregion to around 2.5 million DALYs in African and Southeast Asian subregions. Iron fortification is found to be economically more attractive than iron supplementation.
Ma et al. (2008)[18]	General population	Cost effectiveness analysis	Iron and zinc fortification vs. no fortification; dietary diversification	Iron and zinc deficiency	Biofortification showed the lowest costs per capita (I$0.01) among interventions on iron and zinc deficiency; dietary diversification through

					health education represented the highest costs (I$1148); biofortification is especially feasible and cost effective for rural populations
Rouse (2003)[19]	Antenatal population in Zaire, New Guinea, Nepal	RCTs in Zaire and New Guinea; double-blind randomized cluster in Nepal	Iodine supplementation vs. no supplementation (Zaire, New Guinea); vitamin A/β-carotene supplementation vs. no supplementation (Nepal)	Cost effectiveness and standardized cost effectiveness	Iodine supplementation: $1.80 to $18.00/ infant-early child death avoided ($0.09-$0.90 discounted per life-year gained); vitamin A/β-carotene supplementation: $19.00 to $193.00/ infant-early child death avoided ($0.95-$9.50 discounted per life-year gained)
Romano et al. (1995)[20]	General (target pregnant women)	Secondary data from RCTs and other sources	Folic acid supplementation vs. no supplementation	Neural tube defects avoided	Net benefits from fortification of $94 million (B/C ratio 4.3:1) from low-level fortification and $252 million (B/C ratio 6.1:1) from high-level fortification
Llanos et al. (2007)[21]	General population in Chile	Ex-post economic analysis	Folic acid fortification vs. no fortification	Neural tube defects; infant mortality	Intervention costs per neural tube defect case and infant death averted were I$1,200 and I$11,000 respectively; cost per DALY averted was I$89; net cost savings of fortification of I$2.3 million
Bentley et al (2008)[22]	US population subgroups divided by age, gender,	Cost effectiveness analysis	Folic acid fortification of enriched grain products vs. no fortification	Neural tube defects, myocardial infarctions, colon cancers, B12 deficiency maskings	266,649 QALYs gained with US $3.6 billion saved over the long run by increasing fortification levels

	and race/ ethnicity				
Jentink et al. (2008)[23]	Women of child bearing years in Netherlands	Cost effectiveness analysis	Folic acid fortification vs. no fortification	Neural tube defects	Bulk food fortification with folic acid cost effective if enrichment costs remain below € 5.5 million
Fiedler et al. (2009)[24]	General population in 48 countries	Cost effectiveness analysis of 122 interventions	Biofortification with multiple micronutrients vs. no biofortification	Multiple micronutrient deficiency	Most cost effective intervention in each of the 48 countries was identified
Zimmerman et al. (2004)[26]	General population	Scenario approach	Vitamin A biofortification with GM rice vs. no fortification	Vitamin A deficiency	Annual health improvements found to be worth between US $16 million and $88 million; rates of return on R&D range between 66% and 133%
Bouis (2002)[27]	General population in south Asia	Economic simulation model	Effects of investments in plant breeding vs. alternate investments on iron deficiency	Benefit to cost ratio; anemia cases prevented; annual cost	Ratio of 19 for returns to better iron nutrition in humans (internal rate of return 29%); ratio of 79 if benefits to increased agricultural productivity are included (internal rate of return 44%); 44 million cases of anemia prevented over 25 years if improved varieties planted on 10% of rice & wheat areas in Bangladesh & India; total cost of $1/anemia case prevented
Meenakshi et al. (2010)[29]	General population in several countries	Cost effectiveness analysis	Biofortification of several crops vs. fortification and supplementation	Multiple micronutrient deficiencies	Most costs per DALY saved through biofortification are highly cost effective with benefit:cost ratios over 1.0 in

					all but one case; biofortification is more cost effective than fortification or supplementation
Stein et al. (2006)[30]	General population in India	Economic simulation and cost effectiveness analysis	Vitamin A biofortification of GM rice vs. no fortification	Vitamin A deficiency	Cost per DALY saved by use of golden rice ranged from US $3.06 (high impact scenario) to $19.40 (low impact) scenario
Stein et al. (2007)[31]	General population in India	Dose response function	Zinc biofortification vs. no biofortification	Zinc deficiency	Zinc biofortification of rice and wheat could reduce burden of zinc deficiency by 20% to 51% and save 0.6 to 1.4 million DALYs each year; cost to save one DALY found to be US $0.73 to $7.31
Stein et al. (2008)[32]	General population in India	Cost benefit analysis	Iron biofortification of rice and wheat vs. no biofortification	Iron deficiency	Iron biofortification of rice and wheat can reduce lost DALYs by between 19% with a cost per DALY saved of US $5.39 (pessimistic scenario) and 58% with a cost per DALY saved of US$0.46
Dalziel et al. (2009)[33]	Women capable of or planning a pregnancy in Australia and New Zealand	Secondary data from published RCTs	Set of intervention options promoting folic acid/folate consumption	Neural tube defects	Population-wide campaigns promoting use of supplements and mandatory supplement use most effective at reducing neural tube defects; population wide and targeted approaches were cost effective, as was extending voluntary fortification, but

					mandatory fortification was not cost effective; promoting a folate-rich diet was least cost effective
Fiedler et al. (2010)[34]	General population in Uganda	Cost effectiveness analysis	Vitamin A fortification of food oil and sugar vs. no fortification	Vitamin A deficiency	Cost per DALY averted is US $82 for sugar fortification and US $18 for oil; vitamin A fortification of vegetable oil is thus 4.6 times more cost effective than of sugar
Manyong et al. (2004) [35]	Children and pregnant/ lactating women in Nigeria	Ex-ante evaluation based on secondary data	Impact of vitamin A fortified cassava on vitamin A deficiency vs. no fortification	Vitamin A deficiency	Internal rate of return from biofortification program would range between 92.4% (pessimistic) and 165.3% (optimistic), representing gains of between $10 million and $63 million annually
Chow et al. (2010)[36]	General population in India	Cost effectiveness analysis	Biofortification of GM mustard vs. high-dose vitamin A supplementation vs. industrial fortification of mustard oil	Vitamin A deficiency	Expanding vitamin A supplementation was least costly ($23-$50 per DALY averted and $1,000 to $6,000 per death averted); GM fortification would avert 5-6 million more DALYs and 8,000-46,000 more deaths but was 5 times more costly; industrial fortification was dominated by both GM fortification and supplementation
Sharieff et al. (2008)[37]	Children in Karachi,	Cost benefit analysis	Iron biofortification vs. no biofortification	Reduction in diarrhea and improvement in	Present value of incremental benefit calculated to be US

	Pakistan			hemoglobin concentrations	$106, indicating home fortification may improve clinical outcomes at a reasonable cost

Table 3 **Economic studies of dietary improvements**					
Reference	Population	Study Design	Intervention/comparison	Outcome(s) measured	Economic findings
Dalziel et al. (2007)[7]	General population in various countries	Cost effectiveness analysis based on trial results; modeled cost utility analysis	10 nutrition interventions	Various depending on study	Cost effectiveness analysis yielded differential costs between AU $0.24/person (Multi Media 2 fruit 5 veg Campaign) and $1,203/person (nurse counseling in GP); cost utility was between AU $46 (Multi Media 2 fruit 5 veg Campaign) and $19,800 (work force group Gutbusters Workplace)
Frazao (1999)[40]	General population in US	Cost of illness approach	Multiple dietary improvement vs. no dietary change	Reductions in CHD, cancer, stroke, diabetes, hypertension, obesity, osteoporosis	Estimated that healthier diets might prevent US $71 billion per year in medical costs, lost productivity and premature deaths
Oster et al. (1996)[41]	Persons 35-69 years in US with cholesterol levels 5.17 mmol/L or higher who do not have CHD	Secondary data from Framingham study, NHANES study and population data	Dietary saturated fat reduction vs. no reduction	Mortality and morbidity	1% to 3% reduction in saturated fat intake would reduce incidence of CHD by 32,000 events and result in savings of US $1.4 billion to $12.7 billion over 10 years
Bibbins-Domingo et al. (2010)[42]	US general population	CHD policy model based simulation	Reduction of 3 grams/ day in dietary salt compared to other interventions	Reduction in CHD, myocardial infarctions	Reduction in salt intake of 3 g/day would save between 194,000 and 392,000 QALYs annually and between US

					$10 billion and $24 billion in health care costs
Dall et al. (2009a)[43]	US general population	Economic simulation model based on secondary data	Dietary reduction of calories, salt, unsaturated fat vs. no dietary change	Multiple chronic conditions	Permanent reductions in daily intake of 100 kilocalories would save US $58 billion annually; long-term sodium reductions of 400 mg/day would save $2.3 billion annually; reductions of 5 grams/day of saturated fat intake would save $2 billion annually
Dall et al. (2009b)[44]	US general population	Economic simulation model based on secondary data	Dietary reduction in calories and salt vs. no dietary change	Multiple chronic conditions	Permanent reductions in daily intake of 100 kilocalories would increase national productivity by US $45.7 billion annually; long-term sodium reductions of 400 mg/day would increase productivity by $2.5 billion annually
Asaria et al. (2007)[45]	General population in 23 countries	Based on longitudinal study	15% reduction in salt intake vs. normal salt consumption; implementation of four key elements of WHO Framework Convention on Tobacco Control	Reduction in cardiovascular disease and cancer	13.8 million deaths could be averted over the 2006-2015 period; cost would be less than US $0.40/person/year in low and lower middle income countries and between $0.50 and $1.00 in upper middle income countries
Smith-Spangler et	US adults aged 40-85	Markov model with 4 health	2 strategies to reduce sodium intake: gov't/	Incremental costs, QALYs, myocardial	Collaborative strategy that decreases sodium intake by

al. (2010)[46]	years	states	industry collaboration to reduce sodium in processed foods vs. a sodium tax	infarctions averted, strokes averted	9.5% averts 513,885 strokes and 480,358 MIs, increases QALYs by 2.1 million, and saves US $32.1 billion in medical costs; sodium tax reducing sodium intake by 6% increases QALYs by 1.3 million and results in $22.4 billion in cost savings
McCarron et al. (2004)[47]	US adult population	RCTs and prospective longitudinal studies	Increased dairy consumption vs. no increase	Multiple chronic disease reduction	First year healthcare cost savings estimated at US $26 billion; five-year cumulative savings exceed $200 billion
Avenell et al. (2004)[50]	UK subjects with impaired glucose tolerance (IGT)	Markov model based on secondary data and RCT	30% reduction in fat through diet vs. no reduction, also exercise	Obesity and diabetes risk factor reduction	QALY 13,389 British pounds by sixth year after high initial costs per QALY
Dallongeville et al. (2011)[51]	France general population	Monte Carlo simulation based on secondary data	Increased fruit and vegetable consumption vs. no increase	Deaths avoided and life-years saved	Costs per life-year saved are smallest for the information campaign, then value-added tax reduction, then food stamp policy
Nnoaham et al. (2009) [52]	UK general population	Economic model based on consumption data and demand elasticity	Targeted food taxes and/or subsidies vs. no taxes and/or subsidies	Reductions in mortality from cardio vascular disease and cancer	Each of the four policy instruments examined would be economically regressive; use of tax proceeds to subsidize consumption of fruits and vegetables could lead to public health gains
Marshall (2000)[53]	UK general population	Comparison of effects of fiscal	Extension of value-added tax to increased	Reduction in ischaemic heart	Extending the tax to main sources of saturated fats

		food policies	number of foods vs. no extension	disease	would increase overall food expenditures by consumers and be disproportionately difficult for lower-income groups
Mytton et al. (2007)[54]	UK general population	Economic model based on consumption data and elasticity values	Taxing principal sources of dietary fat vs. taxing unhealthy foods based on SSCg3d score vs. taxing foods to achieve best health outcome	Reduction in mortality from cardiovascular disease	Fat taxes have the potential to result in a modest reduction in mortality; however poorly designed taxes have the potential to adversely affect consumption of healthy foods
Cash et al. (2005)[55]	US general population	Empirical simulations using Continuing Study of Food Intake by Individuals data	Subsidies for consumption of fruits and vegetables vs. no subsidies	Reduction in incidence of CHD and ischemic stroke	Present value of cost per life saved due to thin subsidies US $1.8 million for vegetables alone; $2.19 million for fruit alone; $1.29 for fruits and vegetables; results vary by low, medium and high income households
Variyam et al. (2006)[56]	Non-Hispanic Caucasian US adults	Difference in differences method based on survey results	Before and after Nutrition Labeling and Information Act (NLEA)	Body weight and probability of obesity	Total monetary benefit of decrease in body weight between US $63 billion and $166 billion, well exceeding program costs
Magnus et al. (2009)[57]	Australian children 5-14 years	Extrapolations based on RCTs, cross-sectional and longitudinal studies	Banning ads for energy-dense, nutrient-poor food and beverages during peak children's TV viewing times	Changes in BMI; DALYs saved	Intervention yielded a gross incremental cost effectiveness ratio of AU $3.70; 37,000 total DALYs were saved; present value of future health care costs saved was $300 million

Gray et al. (2006)[58]	Canada general population	Cost benefit analysis based on secondary data	Trans fat ban vs. voluntary labeling system vs. mandatory labeling system	Economic gains to government (healthcare provider) and costs to food industry	Benefit/cost ratio best estimate of 20.8/1 for trans fat ban (range 2.6/1 to 51.5/1); 20.4/1 for voluntary labeling (range 2.5/1 to 40.3/1); 19.1/1 for mandatory labeling (range 2.4/1 to 47.1/1)
Sacks et al. (2010)[59]	Adult population of Australia	Cost effectiveness analysis	Traffic light nutrition labeling vs. junk food tax	Population weight and body mass index reductions; DALYs averted	Both interventions resulted in reduced mean weight and DALYs averted; cost effectiveness analysis showed both were dominant (effective and cost saving)
Rajgopal et al. (2002)[60]	3,100 limited income adults in US state of Virginia having previously participated in the Expanded Food and Nutrition Education Program (EFNEP)	Cost benefit analysis	Prior participation in EFNEP vs. no participation	Prevention of diet-related chronic diseases/conditions	Initial benefit/cost ratio of 10.64:1; sensitivity analyses yield estimates between 2.66:1 and 17.04:1
Schuster et al. (2003)[61]	368 limited income adults in US state of Iowa having previously	Cost benefit analysis	Prior participation in EFNEP vs. no participation	Cost-benefit ratio and several sensitivity analyses	1:3.63 cost:benefit ratio

	participated in the Expanded Food and Nutrition Education Program (EFNEP)				
Wessman et al. (2001)[62]	Limited income adults in US state of Iowa having previously participated in the Expanded Food and Nutrition Education Program (EFNEP)	Cost benefit analysis	Prior participation in EFNEP vs. no participation	Prevention of three types of diseases: Type A (life threatening), Type B (non life threatening), Type C (conditions requiring one-time treatment)	Iowa EFNEP generates a benefit:cost ratio of 10.75:1; total EFNEP benefits over September 1998 to February 2000 period of US $14.3 million compared to costs of $1.3 million
Dollahite et al. (2008)[63]	5,730 low income New York state residents	Pretest, posttest design with epidemiological modeling approach	Series of 6 or more food/nutrition lessons	Cost, health benefits in QALYs, monetized benefits	Total program costs were US $892/graduate; 245 QALYs saved at a mean of $20,863/ QALY; society WTP benefit: cost ratio 9.58:1
Gans et al. (2006)[65]	10,144 New England participants including 1,425 Hispanics	Randomized trial based cost effectiveness study	Six minimal contact nutrition interventions	Total blood cholesterol levels using fingerstick methods	Total costs increased as experimental condition intensity increased
Dalziel et al. (2006)[66]	Lyon Diet Heart Study	Cost utility analysis	Mediterranean diet vs. prudent Western diet	Morbidity and mortality from CHD	Mediterranean diet vs. prudent Western diet

	participants (605 patients mean age 54 years)			events	estimated to cost AU $1,013/ QALY gained/person; mean life year gain of 0.31/person; mean QALY gain of 0.40/ person
Panagiotakos et al. (2007)[67]	3,042 adults in Greece with no clinical evidence of CVD	Cross sectional study with a questionnaire	Adherence to Mediterranean diet vs. no adherence	CHD	Total health care cost estimated at 336 Euros for those further away from Mediterranean diet compared to 36 Euros for those who were closer; incremental cost effectiveness ratio was 50.99
Daviglus et al. (2010)[68]	Eligible surviving participants (> 65 yrs) from Chicago Western Electric Study	Longitudinal based	3 strata of fruit and vegetable intake: 14 cups/month (low); 14-42 cups/month (medium); > 42 cups/ month (high)	Cardiovascular disease and cancer	Annual Medicare charges were higher for those with lower intake of fruits and vegetables: US $4,223 vs. $3,128 (CVD); $1,640 vs. $1,352 (cancer); $12,211 vs. $10,024 (total)
Gundgaard et al. (2003)[69]	20% sample of Danish population followed 1993 to 1997	Based on a longitudinal study	Increased intake of fruits and vegetables to meet dietary recommendations vs. baseline intake	Morbidity and mortality from cancers	Simulated intakes of 400 grams and 500 grams per day increased life expectancy by 0.8 and 1.3 years, respectively; heathcare savings from lower cancer incidence were offset by increased life length
Walker et al. (2009)[70]	Older population in Santiago, Chile	Economic evaluation to accompany CENEX study	Programme for complementary food in older people	Pneumonia incidence, walking capacity, and body mass index	Ingredients approach to calculation of medical and non-medical costs borne by patients and society (planned study)

Tomson et al. (1995)[71]	Subjects with total cholesterol between 7.0 and 7.8 mmol/L without ischaemic heart disease or diabetes mellitus	RCT	Medium-intensity strategy following Swedish guidelines for non-pharmacological treatment of hypercholesterolaemia vs. low-intensity strategy	Serum cholesterol and costs of intervention	Both strategies resulted in low reductions in total cholesterol; there was no statistical difference between the interventions; per-subject cost was SEK 753 in the low-intensity group and SEK 3614 in the medium-intensity group

Table 4 **Economic studies of functional foods**					
Reference	Population	Study Design	Intervention/comparison	Outcome(s) measured	Economic findings
Tice et al. (2001)[72]	US general population targeted at those with hyperhomocyst-enemia	Cost effectiveness analysis using Coronary Heart Disease Policy Model	Hypothetical diet fortified with enriched grains to increase folic acid by 100 microg/day vs. vitamin therapy consisting of 1 mg folic acid and 0.5 mg cyanocobalamin/day vs. no fortification	Incidence of myocardial infarction and death from CHD; QALYs saved; medical costs	Providing vitamin supplementation plus grain fortification to men at/over 45 years without CHD would save more than 300,000 QALYs and save over US $2 billion in health care costs
Gerber et al. (2006)[73]	German general population	Cost benefit analysis with Markov model	Consumption of plant sterol enriched margarine vs. no consumption	CHD mortality and morbidity	10-year CHD costs estimated at 696 Euro for population consuming PS margarine vs. 748 Euro for control group; sensitivity analysis estimated savings between 32 Euro and 74 Euro; 10-year reduction in CHD cases of 117,000 and cost reduction of 1.3 billion Euro
Martikainen et al. (2007)[74]	Finnish men and women ages 30, 40, 50, 60	Cost effectiveness analysis using Bayesian modeling	Consumption of plant stanol esters in spread vs. no consumption	CHD prevention	Base case per QALY life years gained ranged between 7,436 and 20,999 Euros for men and between 34,327 and 112,151 Euros for women based on the initial starting age.
Gyles et al. (2010)[75]	Canadian general population	Modified cost of illness approach	Increased consumption of foods enriched with plant sterols vs. no	CHD reduction	Annual healthcare cost savings between CAD $38 million (pessimistic

			consumption		scenario) and $2.45 billion (ideal scenario)
Malla et al. (2007)[76]	Canadian general population	Cost of illness approach	Consumption of trans fat free canola oil vs. no consumption	CHD reduction	Annual CHD cost savings between CAD $54.5 million (extreme low case) and $441.5 million (high case)
Schmier et al. (2006)[77]	US male population having suffered myocardian infarction	Decision analytic model	Omega-3 supplementation vs. no supplementation	Deaths delayed, cost per death delayed, fatal MIs avoided, cost per fatal MI avoided	Use of omega-3 supplements results in fewer fatal MIs and CVD deaths in short and long term analyses. Supplementation is cost-effective and cost-saving, yielding better outcomes at lower costs.
Coyte (2005)[78]	Canadian general population	Economic burden of illness approach	Increased consumption of flax products vs. no increase in consumption	CVD, type 2 diabetes	Health economic benefits range for CVD range from CAD $1,186.2 million (base case estimates) to $3,558.6 million (best case estimates), and for type 2 diabetes range from $47.6 million (base case estimates) to $142.7 million (best case estimates)

Figure 1 **Search strategy flow chart**