The value of food

Savoir vivre = savoir manger

Irene Lenoir-Wijnkoop

The value of food

Savoir vivre = savoir manger

Irene Lenoir-Wijnkoop

Colophon
The value of food – *Savoir vivre* = *savoir manger*

Cover design: Tony Trichard

Printed by: Optima Grafische Communicatie (www.ogc.nl)
ISBN: 978-94-6361-729-1
DOI: https://doi.org/10.33540/1456

The value of food

Savoir vivre = savoir manger

De waarde van voeding

(met een samenvatting in het Nederlands)

(avec un résumé en français)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
maandag 26 september 2022 des middags te 12.15 uur

door

Paula Irene Lenoir-Wijnkoop

geboren op 26 september 1954 te Oss

Promotoren:
Prof. dr. J. Garssen
Prof. dr. H.J.H.M. Claassen

Beoordelingscommissie:
Prof. dr. A.D. Kraneveld
Prof. S. Lebeer
Prof. dr. R.F. Witkamp
Prof. dr. E.M. van der Beek
Dr. L.H.M. van de Burgwal

TABLE OF CONTENTS

Chapter 1

General introduction

BACKGROUND

The topics food, diet and nutrition are related to many different fields. Food, as basic need for any human being, is included in the Universal Declaration of Human Rights as part of the "*standard of living adequate for the health and well-being of himself and of his family*" (UN 1948). It is generally acknowledged that eating habits find their roots in a combination of factors. For long, food intake was primarily driven by the necessity to fuel the body with sufficient energy for carrying out daily activities and humans took their food where they could find it, without wondering much about quality or digestibility, learning through trial and error.

A more stable food supply became available when people started to cultivate wild plants, roughly 23 thousand years ago.[2,3] This ultimately laid the foundation of agriculture, after a slow and long-lasting process that unfolded simultaneously in different parts of the world, sometimes in a very different manner. Together with the domestication of animals, it allowed a better control of food resources.[4] Although food supply remained for a long period of time mostly dictated by the nearby collection and harvest of edibles obtained from agriculture, livestock or fisheries, the possibility to store food combined with increasing abilities of transformation and conservation marked a turning point in human living conditions. Demographic growth, the gradual change from rural life to urbanization, the development of industrialized societies reshaped the nature and organization of daily food supplies with far-reaching implications for today's eating patterns.

NUTRITION AND HEALTH

The early awareness that nutrition directly affects health resulted from the first rational approach towards diseases, longtime seen as a punishment of the gods.[5] From the ancestral practices and traditions up to now, the development of the science of nutrition has been and still is a fascinating story, where major advances in understanding and knowledge took place in reaction to various non-scientific events, such as geographical explorations, religions, wars and other sociopolitical issues;[6-8] external factors that in the first instance do not have a link with the discipline of nutrition.

Groundbreaking progress developed during the second half of the nineteenth and the first part of the twentieth century. The lack of specific food compounds led to a key observation in the etiology of diseases such as scurvy, beriberi, pellagra and many other deficiency diseases related to an insufficient intake of minerals and/or vitamins.[9-11]

This, as well as food scarcity and famine during the two world wars in the first half of the twentieth century, inspired the early nutritional guidance with the aim to avoid starvation, undernourishment and nutrient-related deficiency diseases and was determinant for setting the scene of nutrition as a science.[12-14]

More recently, as a result of increasing research on the role of food constituents in physiological processes of the human body, the term functional food emerged. It originated in 1984 when the Ministry of Education, Science and Culture of Japan initiated a series of projects to define new food value criteria, taking into account the so-called primary (basic nutrition), secondary (sensory properties) and tertiary (physiological effects) functions.[15] Functional food was at that time described as "*Food that has physiological functions, including regulation of biorhythms, the nervous system, the immune system, and bodily defence beyond nutrient functions*". Since then, many definitions have been proposed, but until today there is no consensus on an unambiguous definition at international level.[16]

Food industries rapidly identified the concept of health-enhancing foods as a powerful marketing asset and in the nineties communication on specific health benefits as added value of processed products, frequently associated with premium prices, started to invade the food advertisements. Functional foods became a central part of many business strategies, although the proclaimed benefits were not necessarily underpinned with data based on robust scientific evidence.

In this context, food safety agencies and other authoritative bodies decided to elaborate regulatory directives and adapt the existing legislation as to frame the use of nutritional health claims in order to impede promotional communications on non-proven health effects of food products and thus protect the general public against unjustified or misleading advertisement.

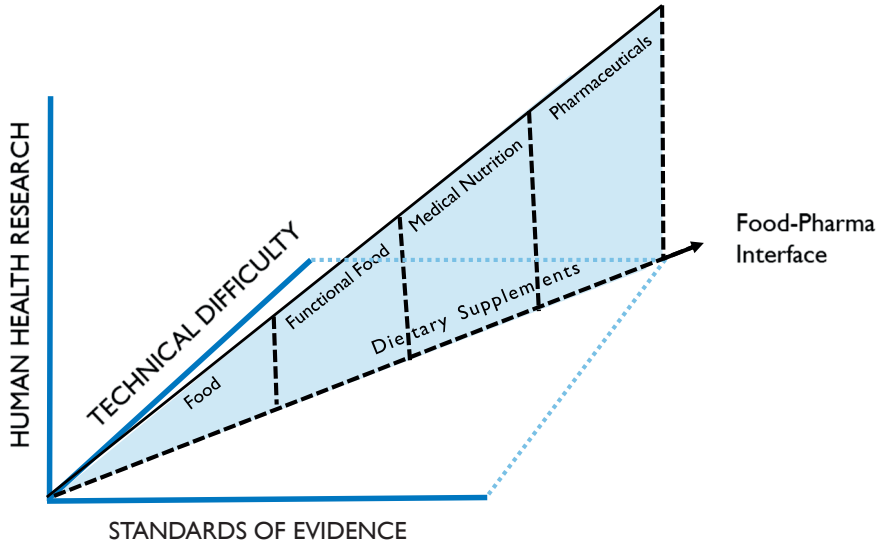
Nevertheless, however laudable the intentions, due to complexity of the various regulations and broad margins for interpretation, claims that can currently be found on the market are not necessarily correlated with nutritional quality and healthy food products.[17,18]

An industrial perspective on nutritional claims

The new legislative provisions with their requirements to seek formal approval for nutritional health claims pushed food manufacturers to extend their usual research activities, until then mainly focused on improving organoleptic and texture properties, preservation methods and other technological aspects. R&D departments needed a new kind of expertise to demonstrate the health impact of a food product, of an added

ingredient or of a specific process. Except for a few, food companies were unfamiliar with the field of human health research, the associated premarketing investments and the relatively long timespan of investigation it implies. Nonetheless, the challenges were faced with assertiveness and confidence, there was a considerable increase in the levels of resources allocated to R&D activities. New positions in clinical nutrition research, in biostatistics etc. were created as well as new skills related to the development, marketing and tracing of nutritional placebos for conducting double blind trials on food and medical nutrition products. In parallel, pharmaceutical companies, already experienced in the subject matter and the operative methodologies of good manufacturing practices of nutrient containing substances, realized that the diversification from drug screening, development and heavy marketing authorizations towards the field of food supplements and alternative forms of nutritional support offered a lucrative opportunity to pluck some low-hanging fruit. Vitamin pills and other dietary supplements were already part of existing product lines and widely on display in pharmacies and drugstores.[19] Not only consumers were familiar with these products, purchased on medical prescription or as OTC products and often considered beneficial for health as a matter of course, but also the standard conditions for commercializing these non-drug supplements appeared to be far less constraining than for a (functional) food bearing a claim (Figure 1).[20-22, 24]

Figure 1. Industrial perspective on nutritional claims (Adapted from Weenen[24])



In the years prior to the entry into force of the regulation (EC) No 1924/2006 on nutrition and health claims made on foods,[23] many food companies decided to keep ahead of the future regulatory environment. It was generally believed that the required evidence of

health effects would be sufficiently demonstrated through clinical trials of good quality. The skills and knowledge needed to conduct such trials were readily available at medical research organizations and within pharmaceutical R&D departments and could rapidly be internalized to ensure a competitive advantage.

The fact that randomized controlled trials (RCT) and accompanying methodologies might not represent the most appropriate way to demonstrate nutritional benefits on population level was at that point in time not questioned.[25] As newcomers in this field of health research, food companies did not envisage to lose time on developing tools in adequacy with the specificities of daily food products; perhaps any doubt never crossed their mind back then. Sooner or later food and beverages companies discovered that sufficient and convincing clinical evidence could not be generated as easily as anticipated in the optimistic beginnings.[26,27] In spite of the considerable increase of R&D resources, the outcomes of expensive and lengthy clinical trials did not necessarily reach the high expectations. Requirements for complying to the regulation were often insufficiently understood or not clearly defined.[28] In many cases the process of building an application file providing the required scientific level appeared to be an insurmountable hurdle, partly due to the complexity of the process, and obtention of the much-coveted approval failed.[29,30]

OUTLINE OF THE DISSERTATION

The above-mentioned situation inspired the idea of the current thesis: personal observations led to the conclusion that addressing the area of nutritional health effects for the general population through the lens of methods and standards applicable to clinico-pharmacological research presented some serious limitations. When conducting trials in the field of (clinical) nutrition, the existing RCT principles and associated statistical analyses for research may provide a reliable evidence-base for demonstrating nutritional health effects in well-identified populations under controlled conditions. But even the most rigorous setting will not allow to capture the multiple interactions between food constituents and their many different targets in the human body, involving a high number of interdependent physiological and metabolic processes, nor the occurrence of very small effects and related health changes only observable over the long term.[31]

Approved claims can influence consumer choices,[32] however this does not imply that the consumer gets useful and understandable information enabling him/her to appropriate food purchase and healthy eating habits.[33,34] Health authorities are well aware that unhealthy food behaviour exerts an increasing pressure on the available healthcare

resources and while claims regulation allows, in principle, to ensure responsible marketing by food manufacturers and to avoid unsubstantiated or misleading claims, it does not offer a structure to evaluate the impact of food patterns on public health issues in spite of clear needs and important stakes going from direct consumer interests to policymaker decisions. Risk assessment and value assessment models exist in different areas. The pharmaceutical industry and the medical community have introduced health economic evaluations to get better insight in optimal resource allocation among various treatment modalities and different disease areas or outcomes.[35]

It was hypothesized that by creating a new branch of health economics, encompassing the multi-dimensional characteristics of nutrition, it would become possible to develop the appropriate methodology for generating and quantifying reliable cost-effectiveness data and to translate health effects of daily food (both conventional and functional) consumption into evidence-informed outcomes, both from a healthcare as well as from a consumer perspective.

In order to assess the feasibility of building the intended connection between the health economic principles and the field of nutrition, ten specialists from clinical, pharmacological and health economic disciplines convened in a panel discussion with the objective to clarify the scope and identify the key issues that should be taken into consideration. It engendered a new subdiscipline that they decided to name Nutrition Economics, defined as "*The discipline dedicated to researching and characterizing health and economic outcomes in nutrition for the benefit of society*." Eighteen months later the group gathered again in a similar format to continue the debate and further reflect on a number of methodological questions and additional key aspects related to the challenge raised by the translation of nutrition-related research data into public health decision making. The consensus reached during these two meetings are reported in respectively **chapters 2 and 3**.

During that same period efforts were undertaken to perform a proof-of-concept study in a selected group of non-diseased individuals, receiving a food product with clinically proven health-enhancing properties, presented in **chapter 4**. An issue in nutrition economic assessments lies on one hand in the difficulty to attribute the studied health effect to one well-identified substance within the infinite variety of daily ingested food items and, on the other hand, in the measurement of health-maintenance in the absence of illness. These obstacles were circumvented by investigating a specific mixture of prebiotics in a cohort of healthy infants at-risk for atopic dermatitis owing to a parental history of this inflammatory skin disease, allergic rhinitis, or asthma in either mother or father. A nutritional cost-effectiveness model using decision analytical techniques was

created. This pilot study confirmed the pertinence of the nutrition economic modelling approach. The outcomes of using of the prebiotic food ingredient for the primary prevention in children at risk for atopic dermatitis, appeared to be highly cost-effective showing positive short- and long-term health economic benefits.

In **chapter 5** the relevance of translating the effects of nutrition into their potential contribution in the containment of the steadily increasing public health burden is addressed. The key points are illustrated from three different perspectives: (i) alleviating undernutrition and nutrient deficiencies, (ii) enhancing conventional foods and (iii) offering selected functional foods. This chapter underlines the importance to improve among health authorities the awareness of nutrition economic modelling as a powerful tool in informing the desirable policy directions. Quantification of the considerable benefits of better-quality diets offers a substantiated rational for implementing cost-effective nutrition interventions.

Chapter 6 focuses on osteoporosis and on a very common food stuff consumed by many people throughout the Western world as part of their daily diet: dairy products. Health benefits of dairy foods, which provide a large variety of essential nutrients such as proteins, minerals, and vitamins, are widely recognized. The aim of this study was to quantify the burden of osteoporosis (in terms of costs and health outcomes) and to estimate the impact of increasing dairy foods consumption on reducing the occurrence of osteoporotic fractures and related costs and loss of quality of life in elderly. The analysis concludes that the societal burden of hip fractures associated with low calcium intake is quite substantial. The findings support the use of a food-based approach to help maintain bone health or prevent age-related bone loss, thus improving quality of life and autonomy in elderly while reducing the associated healthcare expenditures.

Another prevalent health problem, that concerns young and old, preventable through modification of food patterns, both in industrialized countries as well as in developing countries, is overweight, a condition which bears an increased risk of developing obesity and type 2 diabetes. A population group of particular interest in the context of overweight and its consequences are women of childbearing age. An area rather neglected in health economics, pregnancy being only a temporary physiological condition and covering a relatively limited number of individuals in comparison to other population groups that include both males and females; a bogus reasoning that overlooks the fact that each and every of the almost 8 billion world citizens originates from a pregnancy and that in the next generation of mothers -today's children aged five to nineteen years- obesity has risen tenfold in the past four decades.[36]

Besides the well-known perinatal morbidities as a result of overweight in the mother,[37,38] more and more evidence is accumulating on the long-term risks of developing not only type 2 diabetes but also diseases as cancer, cardiovascular diseases and other health impairment in the offspring,[39-41] and even in the following generations.[42,43] A worrisome perspective according to the data analysed in **Chapter 7** which elaborates on a nutrition economic framework for the estimation of the already existing healthcare burden associated with maternal overweight and/or gestational diabetes mellitus. The presented outcomes underline the need for preventive management strategies and public health interventions on lifestyle and diet.

In line with this and to further quantify the socioeconomic threat in this area and propose affordable ways to curb the curve, **Chapter 8** explores the potential economic benefit of an increase in yoghurt consumption in the general population as a preventative measure against the development of type 2 diabetes. A large meta-analysis has linked the daily consumption of yogurt to a lower risk of developing type 2 diabetes, an association that was not reported for the intake of other dairy products.[44] The model incorporates the different stages of disease evolution, including the risk of developing diabetes-related complications and the loss of quality of life over time, on the level of the average population. Given the rapidly increasing prevalence of type 2 diabetes, the findings of this research offer implications for cost saving measures which could help alleviate the socioeconomic burden and relieve the pressure on healthcare infrastructures of this rapidly expanding non-communicable disease.[45]

It is tempting to imagine that non-communicable diseases and the other health concerns discussed so far will not really touch “you and me”, people reasonable and responsible enough for avoiding regular overeating and excessive sedentary lifestyle. Nothing could be further from the truth, often these personal assumptions turn out to be mistaken. However, when proposing an innovative concept, as is the case for nutrition economics, the hurdle of convincing and enthralling the major stakeholder parties is high. Therefore, **chapter 9** offers a very different example which, at first face, has nothing to do with eating habits, namely influenza-like illnessess (ILI) commonly called flu, a virus infection everybody is familiar with and gets exposed to. Treatment mostly relies on symptom control, but even in times of moderate contamination, outpatient consultation rates, medical prescriptions and purchase of over-the-counter medication rise considerably; while absence from work or school affects productivity and family life. Therefore, the impact of these very common seasonal respiratory infections on socioeconomic level is substantial and given the lack of satisfactory treatments, prevention is the cornerstone of ILI management.[46,47] Many scientists report that the consumption of probiotics[48] reduce the duration and frequency of ILI, findings confirmed in two meta-analyses. On the basis

of these data a microsimulation model was designed. The model has been populated with a study cohort, consisting of a representative sample for a given country in terms of demographics, incidence and known ILI-related risk factors. The chapter describes the initial modelling approach as well as two follow-up studies, taking into account the country specificities of three different national health systems, France, Canada and the United States respectively. Identifying similarities and discrepancies among the three countries also allowed to test and confirm the robustness of the developed methodology.

The first part of **chapter 10** traces the evolution of nutrition economics since its initial introduction in 2011 by analysing the scientific literature on the subject and the parties involved in related fields where the discipline gradually made its entry throughout the period January 2012-December 2021. A short overview of the different study topics is provided and existing barriers are identified and discussed. The second part of this chapter outlines a perspective for further development of nutrition economics in the coming years, in the face of the steadily increasing prevalence of chronic disease conditions associated with daily eating behaviour and other lifestyle patterns. A situation which endangers the sustainability of health structures, the wellbeing of the general population as also of the individual citizen. The integration of citizen science in the field of nutrition economics is proposed as a new way forward to promote healthy eating and balanced food habits more efficiently.

REFERENCES

1 Universal Declaration of Human Rights. United Nations General Assembly, Paris 1948. http://www.ohchr.org/EN/UDHR/Documents/UDHR_Translations/eng.pdf

2 Piperno DR, Weiss E, Holst I, Nadel D. (2004) Processing of wild cereal grains in the Upper Palaeolithic revealed by starch grain analysis. *Nature* 430 (7000), 670-673. doi:10.1038/nature02734

3 Snir A, Nadel D, Groman-Yaroslavski I, Melamed Y, Sternberg M, Bar-Yosef O, Weiss E (2015) The Origin of Cultivation and Proto-Weeds, Long Before Neolithic Farming *PLoS One* 10(7), e0131422. doi:10.1371/journal.pone.0131422

4 Gupta AK. (2004) Origin of agriculture and domestication of plants and animals linked to early Holocene climate amelioration. *Current science*, 87(1), 54-59.

5 Santacroce L, Bottalico L, Charitos IA. (2017) Greek Medicine Practice at Ancient Rome: The Physician Molecularist Asclepiades. *Medicines* (Basel) 4(4), 92. doi:10.3390/medicines4040092

6 Nunn N, Qian N. (2010) The Columbian Exchange: A History of Disease, Food, and Ideas. *Journal of Economic Perspectives* 24(2), 163-188.

7 Meyer-Rochow VB. (2009) Food taboos: their origins and purposes. *J Ethnobiol Ethnomed*. 29(5), 18. doi:10.1186/1746-4269-5-18

8 Appert N. (1810) L'art de conserver, pendant plusieurs années, toutes les substances animales et végétales [The art of preserving all kinds of animal and vegetable substances for several years]. Source gallica.bnf.fr / Bibliothèque nationale de France.

9 Tellingen van C. (2010) Het scheepsjournaal van Ellerbeek: gezond verstand en serendipiteit bij de behandeling van scheurbuik. *Ned Tijdschr Geneeskd*. 154, A1881.

10 Sutton G. (2003) Putrid gums and 'dead men's cloaths': James Lind aboard the Salisbury. *J R Soc Med*. 96(12), 605-608. doi:10.1258/jrsm.96.12.605

11 Semba RD. (2012) The discovery of the vitamins. *Int J Vitam Nutr Res*. 82(5), 310-315. doi:10.1024/0300-9831/a000124

12 Hauber U, Neuhäuser-Berthold M. (1996) Historische Entwicklung von Empfehlungen zur Nährstoffzufuhr [Historical development of dietary recommendations]. Z Ernahrungswiss. 35(2), 157-162. doi:10.1007/BF01622864

13 Jahns L, Davis-Shaw W, Lichtenstein AH, Murphy SP, Conrad Z, Nielsen F. (2018) The History and Future of Dietary Guidance in America. *Adv Nutr*. 1(2), 136-147. doi:10.1093/advances/nmx025

14 Lupton JR, Blumberg JB, L'Abbé M, LeDoux M, Rice HB, von Schacky C, Yaktine A, Griffiths JC. (2016) Nutrient reference value: non-communicable disease endpoints--a conference report. *Eur J Nutr*. 55 Suppl 1, S1-10. doi:10.1007/s00394-016-1195-z

15 Arai S. (1996) Studies on Functional Food in Japan – State of Art. *Biosci. Biotech. Biochem.* 1, 9-15.

16 Doyon M, Labrecque JA. (2008) Functional food: a conceptual definition. *British Food Journal* 110 (11), 1133-1149.

17 André Q, Chandon P, Haws K. (2019) Healthy Through Presence or Absence, Nature or Science? A Framework for Understanding Front-of-Package Food Claims. *Journal of Public Policy & Marketing* 38(2), 172-191.

18 Kušar A, Žmitek K, Lähteenmäki L, Raats MM, Pravst I. (2021). Comparison of requirements for using health claims on foods in the European Union, the USA, Canada, and Australia/New Zealand. *Compr Rev Food Sci Food Saf.* 20, 1307–1332.

19 Top 5 places where U.S. adults purchased dietary supplements in 2016. https://www.statista.com/statistics/308349/top-places-to-purchase-dietary-supplements-among-us-adults/

20 Directive 2002/46/EC of The European Parliament and of The Council. (2002) https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32002L0046
21 Bailey RL. (2020) Current regulatory guidelines and resources to support research of dietary supplements in the United States. *Crit Rev Food Sci Nutr*. 60(2), 298–309. doi:10.1080/10408398.2018.1524364
22 Walji R, Wiktorowicz M. (2013) Governance of natural health products regulation: An iterative process. *Health Policy* 111, 86– 94.
23 Regulation (ec) no 1924/2006 of the European Parliament and of the Council. (2006) *Official Journal of the European Union*. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1924&from=en
24 Weenen TC. (2013) On the Origin and Development of the Medical Nutrition Industry. Doctoral dissertation. Erasmus University Rotterdam.
25 Lappe JM, Heaney RP. (2012) Why randomized controlled trials of calcium and vitamin D sometimes fail. *Dermatoendocrinol*. 4(2), 95-100. doi:10.4161/derm.19833
26 Verhagen H, van Loveren H. (2016) Status of nutrition and health claims in Europe by mid 2015. *Trends in Food Science & Technology* 56, 39-45. https://www.sciencedirect.com/science/article/abs/pii/S0924224415301321
27 de Boer A, Bast A. (2015) Stakeholders' perception of the nutrition and health claim regulation. *Int J Food Sci Nutr*. 66(3), 321-8. doi:10.3109/09637486.2014.986071
28 Martínez SV, Siani A. (2017) Health claims made on food in the EU: The edge between scientific knowledge and regulatory requirements. *Trends in Food Science & Technology* 69, 315-323.
29 Lenssen KGM, Bast A, de Boer A. (2018) Clarifying the health claim assessment procedure of EFSA will benefit functional food innovation. *Journal of Functional Foods* 47, 386–396.
30 Buttriss JL. (2015) Nutrition and health claims in practice. *Nutrition Bulletin* 40, 211–22.
31 Laville M, Segrestin B, Alligier M, Ruano-Rodríguez C, Serra-Majem L, Hiesmayr M, Schols A, La Vecchia C, Boirie Y, Rath A, Neugebauer EAM, Garattini S, Bertele V, Kubiak C, Demotes-Mainard J, Jakobsen JC, Djurisic S, Gluud C. (2017) Evidence-based practice within nutrition: what are the barriers for improving the evidence and how can they be dealt with? *Trials* 18(1), 425. doi:10.1186/s13063-017-2160-8
32 Kaur A, Scarborough P, Rayner M. (2017) A systematic review, and meta-analyses, of the impact of health-related claims on dietary choices. *Int J Behav Nutr Phys Act*. 14, 93.
33 Mariotti F, Kalonji E, Huneau JF, Margaritis I. (2010) Potential pitfalls of health claims from a public health nutrition perspective. *Nutrition Reviews* 68(10), 624–638. doi:10.1111/j.1753-4887.2010.00322
34 Duffy EW, Hall MG, Dillman Carpentier FR, Musicus AA, Meyer ML, Rimm E, Smith Taillie L. (2021) Nutrition Claims on Fruit Drinks are Inconsistent Indicators of Nutritional Profile: A Content Analysis of Fruit Drinks Purchased by Households with Young Children. *J Acad Nutr Diet* 121(1), 36-46. doi:10.1016/j.jand.2020.08.009
35 Jolicoeur LM, Jones-Grizzle AJ, Boyer JG. (1992) Guidelines for performing a pharmacoeconomic analysis. *Am J Hosp Pharm*. 49(7), 1741-7.
36 NCD Risk Factor Collaboration (NCD-RisC). (2012) Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. *Lancet* 390(10113), 2627-2642. doi:10.1016/S0140-6736(17)32129-3.
37 Institute of Medicine/National Research Council. (2009). "Committee to reexamine IOM pregnancy weight guidelines, F.a.N.B.a.B.o.C., youth, and families" in Weight Gain During Pregnancy:

Reexamining the Guidelines, eds K. M.Rasmussen and A.L.Yaktine (Washington, DC: National Academies Press).

38 Bodnar LM, Siega-Riz AM, Simhan HN, Diesel JC, Abrams B. (2010). The impact of exposure misclassification on associations between prepregnancy BMI and adverse pregnancy outcomes. *Obesity* 18, 2184–2190. doi:10.1038/oby.2010.25

39 Moore VM, Davies MJ. (2005) Diet during pregnancy, neonatal outcomes and later health. *Reprod Fertil Dev*. 17(3), 341-8. doi:10.1071/rd04094

40 Barua S, Junaid MA. (2015) Lifestyle, pregnancy and epigenetic effects. *Epigenomics* 7(1), 85-102. doi:10.2217/epi.14.71

41 Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW, Eriksson JG, Broekman BF. (2017) Influence of maternal obesity on the long-term health of offspring. *Lancet Diabetes Endocrinol*. 5(1), 53-64. doi:10.1016/S2213-8587(16)30107-3

42 Catalano PM. (2003). Obesity and Pregnancy the Propagation of a Viscous Cycle? *J Clin.Endocrinol. Metab*. 88, 3505–3506. doi:10.1210/jc.2003-031046

43 Roseboom TJ, Watson ED. (2012). The next generation of disease risk: are the effects of prenatal nutrition transmitted across generations? Evidence from animal and human studies. *Placenta* 33(Suppl.2), 40-44. doi:10.1016/j.placenta.2012.07.018

44 Chen M, Sun Q, Giovannucci E, Mozaffarian D, Manson JE, Willett WC, Hu FB. (2014) Dairy consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. *BMC Med*. 12, 215.

45 IDF Diabetes Atlas 2021. https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf. Accessed 8 March 2022

46 World Health Organization. Influenza (Seasonal) Fact sheet N°211 2014 Available at: https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal)

47 Virk RK, Gunalan V, Tambyah PA. (2016) Influenza infection in human host: challenges in making a better influenza vaccine. *Expert Rev Anti Infect Ther*. 14(4), 365-75. doi:10.1586/14787210.2016.1155450

48 Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, Morelli L, Canani RB, Flint HJ, Salminen S, Calder PC, Sanders ME. Expert consensus document. (2014) The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 11(8), 506-14. doi:10.1038/nrgastro.2014.66

Chapter 2

Nutrition economics – characterising the economic and health impact of nutrition

Irene Lenoir-Wijnkoop, Michel Dapoigny, Dominique Dubois, Eric van Ganse, Iñaki Gutiérrez-Ibarluzea, John Hutton, Peter Jones, Thomas Mittendorf, Marten J Poley, Seppo Salminen, Mark JC Nuijten

Published in: Br J Nutr. 2011;105(1), 157-66

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 the 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.

INTRODUCTION

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 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 pharmaco-economics without modifications. Pharmaco-economics 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 healthcare priority setting. Other features that limit a straightforward use of pharmaco-economic 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 *vs*. 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 *vs*. 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 Authorité 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 tax paying 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.

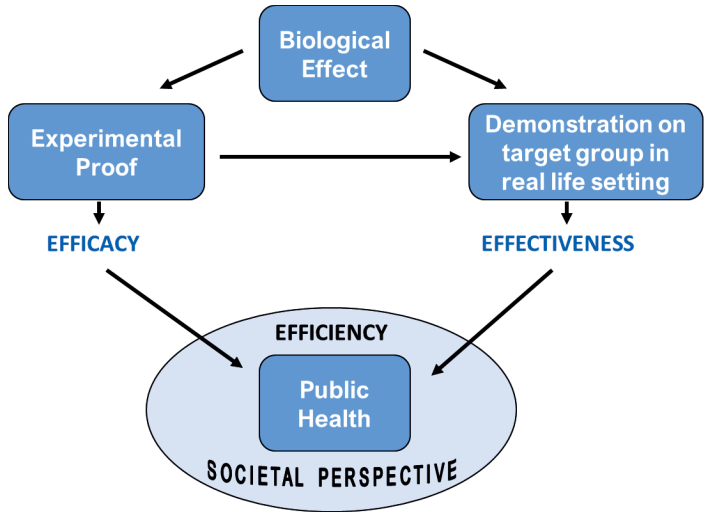
Conclusion: The perspective of nutrition economics needs to be broader than that usually applied in cost-effectiveness analysis in health care.

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 years 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 calcium 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 (Figure 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 represents an essential part of the cost-effectiveness pathway. Adapted study designs will be

Figure 1. The 3-point continuum efficacy, effectiveness and efficiency



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, a 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.

REFERENCES

1 WHO/FAO Expert Consultation (2003) Diet, Nutrition and the Prevention of Chronic Diseases. *Report of a Joint WHO/FAO Expert Consultation*, 1–149. WHO Technical Report Series no. 916. Geneva: World Health Organization.

2 Watson R. (2006) Health spending rising faster than GDP in most rich countries. *BMJ* 333, 60. http://www.bmj.com/cgi/content/full/333/7558/60-a/DC1

3 Health Enhancing Foods. (2006) Agriculture and Rural Development Discussion Paper 30. The Worldbank. http://siteresources.worldbank.org/INTARD/Resources/Health_Enhacing_Foods_ARD_DP_30_final.pdf

4 Functional Food in the European Union. (2008) European Commission, Joint Research Centre, Institute for Prospective Technological Studies. http://ftp.jrc.es/EURdoc/JRC43851.pdf

5 Richtlijnen voor farmaco-economisch onderzoek, College voor zorgverzekeringen, Diemen (2006) Updated version. http://www.cvz.nl

6 Cleemput I, Van Wilder P, Vrijens F, *et al*. (2008) Guidelines for pharmacoeconomic evaluations in Belgium. *Federal Health Care Knowledge Centre KCE Reports* 78C.

7 NICE (2008) Guide to the Methods of Technology Appraisal. http//www.nice.org.uk

8 Edejer TTT, Baltussen R, Adam T, *et a*l. (2003) Making choices in health. WHO Guide to Cost-Effectiveness Analysis. World Health Organization, Geneva.

9 Graf von der Schulenburg JM, Greiner W, Jost F, *et al*. (2008) Hanover Consensus Group. German recommendations on health economic evaluation: third and updated version of the Hanover Consensus. *Value Health* 11, 539–544.

10 McCarron DA, Heaney RP. (2004) Estimated healthcare savings associated with adequate dairy food intake. *Am J Hypertens.* 17, 88–97.

11 Dall TM, Fulgoni VL III, Zhang Y, *et al*. (2009) Potential health benefits and medical cost savings from calorie, sodium, and saturated fat reductions in the American diet. *Am J Health Promot.* 23, 412–422.

12 Dall TM, Fulgoni III VL, Zhang Y, *et al*. (2009) Predicted national productivity implications of calorie and sodium reductions in the American diet. *Am J Health Promot* 23, 423–430.

13 Cox HL, Laupland KB, Manns BJ. (2006) Economic evaluation in critical care medicine. *J Crit Care* 21, 117–124.

14 Heaney RP. (2008) Nutrients, endpoints, and the problem of proof. *J Nutr.* 138, 1591–1595.

15 Heaney RP, Rafferty K. (2009) Preponderance of the evidence, an example from the issue of calcium intake and body composition. *Nutr Rev.* 67, 32–39.

16 Koretz RL. (2005) Nutrition Society Symposium on end points in clinical nutrition trials. Death, morbidity and economics are the only end points for trials. *Proc Nutr Soc.* 64, 277–-284.

17 Wahlqvist ML, Hsu-Hage BH-H, Lukito W. (1999) Clinical trials in nutrition. *Asia Pac J Clin Nutr.* 8, 231–241.

18 Genton L, van Gemert W, Pichard C, *et al*. (2005) Physiological functions should be considered as true endpoints of nutritional intervention studies. *Proc Nutr Soc.* 64, 285–296.

19 Commission Directive (1999) EC of 25 March 1999 on dietary foods for special medical purposes. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31999L0021&from=EN

20 Paré P, Gray J, Lam S, *et a*l. (2006) Health-related quality of life, work productivity, and health care resource utilization of subjects with irritable bowel syndrome: baseline results from LOGIC (Longitudinal Outcomes Study of Gastrointestinal Symptoms in Canada), a naturalistic study. *Clin Ther.* 28, 1726–1735.

21 Ravasco P, Monteiro-Grillo I, Vidal PM, *et al*. (2004) Cancer, disease and nutrition are key determinants of patients' quality of life. *Support Care Cancer* 12, 246–252.
22 NICE (2006) Modelling the cost-effectiveness of physical activity interventions. National Institute for Health and Clinical Excellence. http://www.nice.org.uk/nicemedia/pdf/FourmethodsEconomicModellingReport.pdf
23 Bidlack WR (1996) Interrelationships of food, nutrition, diet and health: The National Association of State Universities and Land Grant Colleges White Paper. *J Am Coll Nutr.* 15, 422–433.
24 Cohen JT, Neumann PJ, Weinstein MC. (2008) Does preventive care save money? Health economics and the presidential candidates. *N Engl J Med.* 358, 661–663.
25 Kahn R, Robertson RM, Smith R, *et a*l. (2008) The impact of prevention on reducing the burden of cardiovascular disease. *Circulation* 118, 576–585.
26 Kim JJ, Goldie SJ. (2008) Health and economic implications of HPV vaccination in the United States. *N Engl J Med.* 359, 821–832.
27 Gliklich RE, Dreyer NA (editors). (2007) Registries Evaluating Patient Outcomes: A User's Guide. Agency for Healthcare Research and Quality.
28 AHRQ Conference on Health Care Data Collection and Reporting – Collecting and Reporting Data for Performance Measurement, Moving Toward Alignment. (2006) *Report of Proceedings*. http://healthit.ahrq.gov/portal/server.pt/gateway/PTARGS_O_227079_O_O_18/AHRQ_DataReport_final.pdf
29 Jacobs P, Bachynsky J, Baladi JF. (1995) A comparative review of pharmacoeconomic guidelines. *Pharmacoeconomics* 8, 182–189.
30 Weinstein MC, Fineberg HV. (1980) *Clinical Decision Analysis*, pp. 228–265. Philadelphia, PA: WB Saunders Co.
31 Suarez FL, Savaiano D, Arbisi P, *et a*l. (1997) Tolerance to the daily ingestion of two cups of milk by individuals claiming lactose intolerance. *Am J Clin Nutr.* 65, 1502–1506.
32 McBean LD, Miller GD. (1998) Allaying fears and fallacies about lactose intolerance. *J Am Diet Assoc.* 98, 671–676.
33 Savaiano DA, Boushey CJ, McCabey GP. (2006) Lactose intolerance symptoms assessed by meta-analysis: a grain of truth that leads to exaggeration. *J Nutr.* 136, 1107–1113.
34 Nicklas TA, Qu H, Hughes SO, *et al*. (2009) Prevalence of self-reported lactose intolerance in a multiethnic sample of adults. *Nutr Today* 44, 222–227.
35 Drummond M, Brixner D, Gold M, *et al*. (2009) (Consensus Development Group) Toward a consensus on the QALY. *Value Health* 12, S31–S35.
36 Rutten-van Mölken M, Van Busschbach J, Rutten F (editors) (2000) From costs to effects: a manual for evaluation studies in health care [in Dutch]. Elsevier Gezondheidszorg.
37 Peter A, Taylor R, Butler J*, et al*. (2003) Returns on Investment in Public Health, an Epidemiological and Economic Analysis. Australian Government. Department of Health and Ageing. http://catalogue.iugm.qc.ca/GED_IUG/192359191053/ReturnsOnHealthInvestments.PDF
38 Claes C, Reinert RR, von der Schulenburg JM. (2009) Cost effectiveness analysis of heptavalent pneumococcal conjugate vaccine in Germany considering herd immunity effects. *Eur J Health Econ*. 10, 25–38.
39 Gravelle H, Smith D. (2000) Discounting for Health Effects in Cost Benefit and Cost Effectiveness Analysis, 20. Centre for Health Economics Technical Paper Series 20.
40 Viscusi WK. (1995) Discounting Health Effects for Medical Decisions. *Valuing Health Care*, 125–147. [FA Sloan, editor]. Cambridge: Cambridge University Press.

41 Sloan FA (1995) Valuing Health Care. Costs, Benefits and Effectiveness of Pharmaceuticals and Other Medical Technologies. Cambridge: Cambridge University Press.
42 Robinson R. (1993) Economic evaluation and health care. What does it mean? *Br Med J.* 307, 670–673.
43 Adams ME, McCall NT, Gray DT, *et al.* (1992) Economic analysis in randomised controlled trials. *Med Care* 30, 231–243.
44 Drummond MF, Davies L. (1991) Economic analysis alongside clinical trials. Revisiting the methodological issues. *Int J Technol Assess Health Care* 7, 561–573.
45 Drummond MF, Ludbrook A, Lowson K, *et al.* (1986) Studies in Economic Appraisal in Health Care, vol. 2. Oxford University Press, Oxford
46 Framingham Heart Study 1951–2010. http://www.framinghamheartstudy.org/biblio/index.html
47 Arriola L, Martinez-Camblor P, Larrañaga N, *et al*. (2010) Alcohol intake and the risk of coronary heart disease in the Spanish EPIC cohort study. *Heart* 96, 124–130.

Chapter 3

Concepts and methods in the economics of nutrition – gateways to better economic evaluation of nutrition interventions

Irene Lenoir-Wijnkoop, Mark JC Nuijten, Iñaki Gutiérrez-Ibarluzea, John Hutton, Marten J Poley, Leonie Segal, Jean-Louis Bresson, Eric van Ganse, Peter Jones, Luis A Moreno, Seppo Salminen, Dominique Dubois

Published in: Br J Nutr. 2012;108(9), 1714-20

ABSTRACT

Improving health through better nutrition of the population may contribute to enhanced efficiency and sustainability of healthcare systems. A recent expert meeting investigated in detail a number of methodological aspects related to the discipline of nutrition economics. The role of nutrition in health maintenance and in the prevention of non-communicable diseases is now generally recognised. However, the main scope of those seeking to contain healthcare expenditures tends to focus on the management of existing chronic diseases. Identifying additional relevant dimensions to measure and the context of use will become increasingly important in selecting and developing outcome measurements for nutrition interventions. The translation of nutrition-related research data into public health guidance raises the challenging issue of carrying out more pragmatic trials in many areas where these would generate the most useful evidence for health policy decision-making. Nutrition exemplifies all the types of interventions and policy, which need evaluating across the health field. There is a need to start actively engaging key stakeholders in order to collect data and to widen health technology assessment approaches for achieving a policy shift from evidence-based medicine to evidence-based decision-making in the field of nutrition.

INTRODUCTION

Escalating healthcare costs have become a major concern for decision makers, prompting development of innovative cost containment measures.[1,2] In Europe, health authorities have started to establish incentives for efficient healthcare delivery by means of decentralisation of the healthcare decision-making process and implementation of market mechanisms.[3] Cost-effectiveness analysis has become common practice for informing reimbursement decisions for pharmaceuticals and other health technologies, including devices.[4] Nutrition interventions tend to be excluded from these processes, although healthcare decision makers have begun to realise that food plays an important role, not only in those already with disease, but also in the onset and evolution of lifestyle-related disorders. Indeed, improving health through better population nutrition may contribute to the cost-effectiveness and sustainability of healthcare systems. It is therefore essential to describe and quantify the costs and effectiveness of nutrition interventions, both the immediate costs of the intervention and downstream consequences, and to assess impacts for individuals, the healthcare system and society as a whole. The discipline of nutrition economics, currently being established, is relevant and timely for informing decision-making. First, this discipline helps to better inform health authorities and consumers on the harms of poor nutrition and on the benefits of making certain food choices. Second, the discipline is essential to governments in designing efficient public population-scaled interventions and educational campaigns. A third focus is on nutrition interventions delaying disease onset or progression. Finally, nutrition economics is also relevant for improving the nutritional quality of foods produced by industry. To identify and explore the field of nutrition economics, a first expert meeting was held in February 2010. This exchange resulted in a consensus about the importance of defining this new area and led to the establishment of a first multidisciplinary approach to understanding the principles, relevance and particular characteristics of the field of nutrition economics.[5] A second meeting was held in Madrid, in October 2011 with the goal to investigate in detail a number of methodological concepts and issues. Nutrition interventions vary from specific individual treatments to broad public health measures, and therefore their evaluation requires a range of different approaches. They depend on involvement of the target audience in the decision to engage in the 'intervention', often without the support provided in adhering to a specific treatment on medical prescription. The feasibility of expressing the multidimensional impact of nutrition on the individual's quality of life in a single outcome measure has yet to be fully addressed. The need to enhance capacity in the evaluation of complex multi-component interventions formed the focus of the panel discussions reported below.

HEALTH ECONOMICS AND NUTRITION

Cost-effectiveness analyses aim to provide reliable, reproducible and verifiable insight into the effectiveness of an intervention, the costs of its implementation and the potential downstream savings. Cost-effectiveness analyses in nutrition interventions tend to rely heavily on health economic modelling, as a long-term follow-up is required to appropriately measure impacts, which invariably extend far beyond the periods of intervention. The challenges of a long-term follow-up are many, including handling of dropouts, study investment costs and changes in technology or society, which can render the original intervention or control context unrealistic. Nutrition interventions are often preventive; they can be implemented at the population level or individually and employ various methods including health promotion, social marketing, consumer research, clinical consultation and financial incentives such as taxes, subsidies or regulations. Nutrition interventions cover the cycle from farm to fork and thus extend well beyond the health sector. Nutrition economics and the economic evaluation of nutrition interventions must therefore deal with a wide range of issues.

Nutrition and health-related quality of life assessment

The concept of health-related quality of life (HRQL) is relevant to health-economic evaluations wherever quality of life impacts are expected, which will typically be the case with nutrition interventions. HRQL is a multidimensional concept and encompasses several aspects including (1) the person's functional status across various domains, such as physical, occupational and interpersonal, and (2) the person's appraisal of how his/her health affects his enjoyment or quality of life.[6] One proposed definition of HRQL is: 'the subjective perception of the impact of health status, including disease and treatment, on physical, psychological, and social functioning and wellbeing'.[7] However, this does not mean that it is a subjective measure. Indeed, a measurement instrument that is validated according to rigorous validity criteria can objectively assess subjective phenomena.[8] In contrast to traditional endpoints used in clinical trials, the responses to quality-of-life questionnaires directly reflect the subject's own perspective on his/her health status. The scope of HRQL measures is not limited to patients with defined symptomatic diseases, but can also be used in a general population setting. These measurements are valuable in providing preference-based 'utility values' used in economic evaluation studies. Several concepts,[9,10] techniques[11,12] and instruments[13,14] are available for assigning a utility value to a particular health state. Validated non-preference-based HRQL measures provide additional information on the subject's own viewpoint on health conditions and their management. The principles of health economic evaluation apply to all health technologies. Thus, it makes sense to establish whether the existing methods provide reliable information on nutrition interventions, before addressing methodological

problems specifically related to the field of nutrition. The different health outcome measures have in common that they ascribe the same weight regardless of who gains the benefit. Equity weighing is possible and has been used,[15] but this does not imply that fairness and equity in health is taken into account automatically.[16] Also, characteristics such as personality, cognitive dysfunction and psychological adaptation to illness may influence how a person responds to the items.[17,18] Notwithstanding the imperfections, these measures are very practical for decision makers. Other issues related to nutrition have remained largely unexplored until today. A nutrition intervention may operate very differently from drug treatment, and this needs to be addressed. Some existing paradigms require adjustment in order to include dimensions that are not captured using traditional measures. Food can serve in a context of prevention, treatment, palliative care, etc., and this will inform the development of an appropriate endpoint model and condition the items to be measured. A few more general considerations were discussed, in particular the need to consider the individual's satisfaction. It is important to have this dimension captured in the matrix for quality-of-life assessment in nutrition. A recent Food and Drug Administration Public workshop on Clinical Trial Outcome Assessments emphasised the need to define the context of use for validating outcome assessments: interestingly, the impact on general life concepts presented included productivity, health status, HRQL as well as satisfaction with health.[19] In addition, many subjects who are not diseased but have a known risk factor, e.g. a high LDL-cholesterol concentration or a low bone mineral density, will prefer not to take drugs to avoid being labelled as a patient or through fear of drug-related adverse effects.[20] The choice not to pursue medication is a component that is often not captured when assessing quality of life, partly because that target population is unlikely to enter a trial. Assessing the HRQL impact of prevention in a sub-healthy individual is extremely relevant in nutrition, since the awareness of being at risk for developing a disease might also affect quality of life.[21]

In summary, for comprehensive outcome measures for nutrition in a daily setting, the appropriate assessment tools have to be selected based on the context and the research question.

Health technology assessment and decision-making

Health technology assessment (HTA) provides evidence and analysis for different levels of decision-making: micro – clinicians, meso – managers; and macro – policymakers. HTA seeks to provide health authorities and professionals with accessible and usable information to guide their decisions, whether these are used for advice on individual technologies or intended as guidelines for the management of health concerns and target populations. The scope of HTA needs to incorporate broad-ranging issues, including social values, legal concerns, ethical aspects and organisational issues, as well

as clinical benefits and cost-effectiveness. The focus of a particular HTA will depend on the decision context – who needs the information and for what type of decision. Properly used, HTA helps to produce transparent, accountable and evidence-based decisions. However, HTA has been mainly associated with drug and medical device reimbursement decisions, where, in many countries, financial considerations of affordability may be as important as clinical and cost-effectiveness. Although a decision-making process in the field of nutrition economics will in general not involve reimbursement for individual products, interventions to change public awareness of, and attitudes to, nutrition will have a cost, which needs to be justified against other uses of health budgets. For example, in the case of initiatives to change eating patterns by introducing taxes on unhealthy or unbalanced food products, the consequences in terms of economic efficiency and social equity need to be carefully evaluated during the decision-making process. Although the intention is to improve public health, the economic consequences of such taxation could induce an opposite effect or lead to increasing health inequalities.[22,23] Another important consideration is the impact of policies which are primarily designed to meet non-health objectives, but which have a major effect on health. In the field of nutrition, there are clear links with agricultural policies. Reports from the European Commission indicate that the health impact of policies is often secondary to economic or regional policy interests[24] and support the idea that health is not necessarily considered in an appropriate manner in impact assessments.[25] These factors offer an interesting opportunity for the application of the HTA evaluation framework in the field of nutrition economics, where equity and efficiency considerations may be equally important. The general population and decision-makers are not only interested in efficiency but also in equity in the distribution of health.[26] Current initiatives to apply comprehensive economic evaluation methods to public health interventions, including those in nutrition, should be continued.[27]

The use of models in the nutrition arena

The use of models in economic evaluation combines different types of data sources to extend available information. Models can be used to simulate costs of trial modalities, to generalise trial results, to translate evidence from randomised clinical trials (RCT) into daily practice or to explore the potential value of additional evidence from empirical research. Several types of models can be used in the area of nutrition. One of them is the decision tree, comparing two or more health strategies. It defines intervention pathways and then links costs and outcomes to all the possible options. Another type of model is the Markov model, organised around health states rather than around pathways.[28] In this case, the data input will be based on probabilities of transitions between successive health states and specific costs and utilities associated with the various health states.[29] Still other modelling techniques that can be used in nutrition economics are methods

that stem from epidemiology, such as the population attributive fraction and the potential impact fraction.[30] Modelling techniques usually extrapolate the available short-term evidence over time in order to estimate outcomes beyond the study period or to link intermediate endpoints to final outcomes. This approach represents a valuable contribution in decision-making processes that face the challenging task of achieving small but tangible modifications of dietary behaviour in order to reduce nutrition-related chronic health concerns on the long term.[31] The need for a long-term follow-up, in the general or in a healthy at-risk population, may be solved by extrapolation methods; these are not specifically related to nutrition, but more to underlying available evidence and relationships. A good illustration can be found in the North Karelia Project. In this Finish province, a major preventive project was launched in the early 1970s with the aim to reduce the high morbidity and mortality associated with CVD. The programme was a result of a petition by representatives of the people, who were concerned about the data from national statistics.[32] The intervention, originally set up for a period of 5 years, became national and led in the late 1980s to an intensified action, when surveys showed that the reduction of blood cholesterol was levelling off. The dietary changes in Finland resulting from the intervention, *i.e*. changes in food supply and nutritional and lifestyle recommendations, have led to an 80% reduction in annual CVD mortality rates among the working-age population, and a major increase in life expectancy has been observed, as well as improvements in functional capacity and health.[33,34] Lifestyle study programmes,[35] cross-sectional surveys[36] and cohort studies[37,38] allow us to develop risk equations for disease progression that include the quality of the diet. The Australian longitudinal study on Women's Health illustrates the opportunity to explore dietary patterns and the relationship between diet and diverse health outcomes, including healthcare costs.[39] The foregoing discussion underlines that evidence requirements have to be fulfilled in two complementary ways: by clinical evidence from RCT and by epidemiological observations and national statistics.

The quality of evidence

Healthcare guidance must be based on best available evidence.[40,41] It is not limited to the clinical situation; often the guidance is intended to other public agencies in the education and social service sectors or directly to individuals. In the case of therapeutic interventions, the properly conducted RCT is commonly recognised as the gold standard for clinical efficacy. This criterion relates to the issue of preferring internal validity to external validity.[42] The difficulty of using a RCT is its translation to the population level and linking results of clinical intervention trials with high internal validity in terms of treatment outcomes in routine practice.[43] This translation is especially challenging in nutrition because of more confounding variables and the greater difficulty in controlling nutritional factors when compared with pharmaceutical treatments. As previously mentioned,[5] the lifestyle

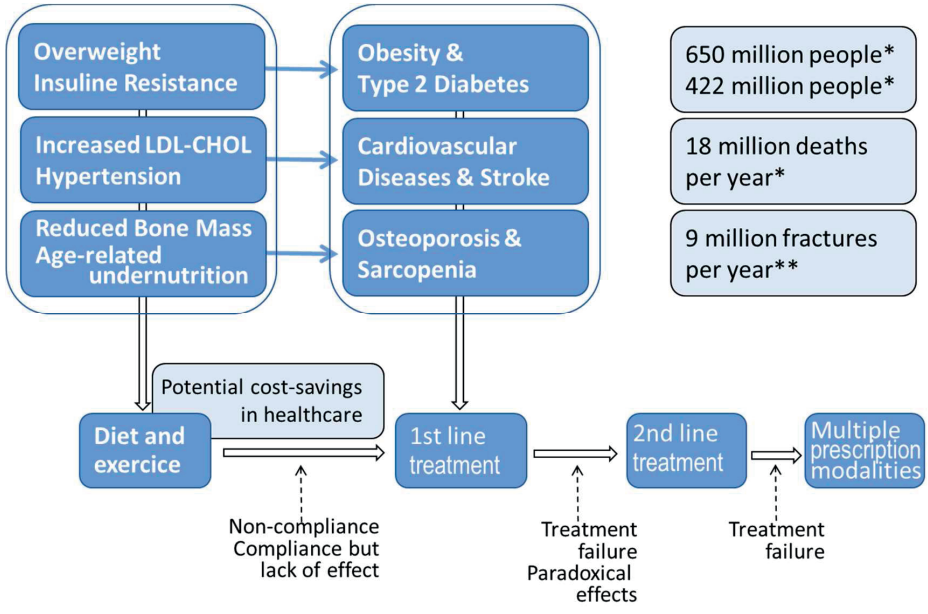
setting and a need for high external validity justify the use of other types of evidence, such as cohort studies and other observational data. Clinical trial populations do not match the population likely to be treated with the study intervention. New methods and new developments have been produced, not as much related to the clinical effect, but more to the clinical relevance and final results on a totality of subjects.[44] It will be of great interest to translate this approach to the field of nutrition economics, where the final endpoint is the relevance for society. The issue is not restricted to defining the level of evidence but also includes translation of the evidence into public health guidance in terms of nutrition interventions, which raises the challenging issue of generalisability to daily practice. To move into the territory of another type of best evidence, a gradual strategy could be considered in order to obtain robust data. Such a strategy begins at the most serious end of a nutrition-related chronic health concern and then is gradually taken upwards. If an effect is observed, the cost of doing so remains limited and when moving further and further up the intervention pathway, the population becomes larger. The research question needs of course to be correctly defined before starting the study and although individual effects might get smaller, the global impact on public health and healthcare expenditures is more likely to attain significance. The process of producing guidance based on the best available evidence is crucial to allow robust and accountable decision-making processes.[45] Nutrition should be no exception to this rule. In recent years, the Grading of Recommendations Assessment, Development and Evaluation approach has been used as a system for rating quality of evidence and strength of recommendations. It is claimed to be explicit, comprehensive, transparent and pragmatic, and is increasingly being adopted by organisations worldwide.[46] The approach is mostly devoted to recommendations for clinical practice and has been applied to recommendations on individuals or health technologies.[47] However, this approach should also be tested in terms of its usefulness for public health interventions and modified accordingly if found to be insufficient.

The importance of evidence-based guidance for nutrition

Clinical guidelines include the role of nutrition in the management of some metabolic diseases, for instance diabetes,[48] but do not routinely do so for other diseases where nutrition can be important. The incorporation of a new intervention modality into clinical guidelines depends on the evidence for the efficacy and safety of a new intervention. The recommendation in clinical guidelines is an important criterion for the choice of prescription modalities by healthcare providers, and if a new intervention strategy is not included in the clinical guidelines, healthcare professionals will be hesitant to apply it. If the guidelines advised consideration of diet and exercise before any drug prescription,[49,50] healthcare costs might be reduced (Figure 1). In producing guidance, cost-effectiveness must also be considered. Escalating costs have resulted in a demand for cost-effectiveness data in the decision-making process. Therefore, interventions

should be assessed on their cost-effectiveness *vs*. standard practice before being included in guidelines.[51]

Figure 1. Common conditions in the general population & treatment pathways – extension of nutritional strategies for managing many non-communicable diseases would considerably reduce healthcare expenditures. (*www.who.int,**www.iofbonehealth.org.)



Some countries have defined a cost-effectiveness threshold in terms of maximum cost per quality adjusted life year (QALY), which interventions must meet before being considered cost-effective and therefore reimbursable. The UK is the only European country to be explicit about the cost-effectiveness threshold it uses. The WHO has proposed thresholds on an arbitrary basis (http://www.who.int/choice/costs/CER_thresholds/en/index.html) and countries may seek to depart from these for various reasons. Countries may also seek to adopt a more complex approach that takes account of other factors such as the type of intervention, the target population, and the quality and certainty of evidence. In reality, in most countries, the health authorities seem to prefer to make decisions without defining clear thresholds or communicate them to the public domain, allowing considerable discretion for policy makers. It is still unclear what would constitute an appropriate cost-effectiveness threshold to apply in a lifestyle-oriented setting.

DISCUSSION – THE FUTURE AGENDA

Nutrition is an aspect of lifestyle and is subject to individual choice. Should society take it into consideration and more actively promote nutrition interventions that improve overall public health and thereby reduce healthcare costs? Should nutrition economics therefore be linked more closely to social values and would these be more relevant than in other fields of health economics? Identifying the concepts to measure and the context of use will be a key consideration in selecting and developing HRQL measurements for nutrition interventions. Satisfaction was frequently mentioned during the meeting and opposing views about the interest of including it in assessments were expressed. Some panel members argued that individual satisfaction is an important driver in motivating people and can therefore improve the impact of public health interventions. Others considered that was not the case, although they conceded that healthy food choices can be enjoyable and help in achieving changes in behaviour. At the moment, nutrition is generally not often taken into account by those seeking to reduce healthcare expenditures. This does not mean that nutrition should necessarily be included in the reimbursement system to attract the attention of decision-makers. By showing the outcomes of some of the measures and strategies already used,[52-55] the nutrition economic approach is likely to quickly gain interest among decision-makers. What is more, current strategies to address the issue of the ageing population and the consequent increasing demands on healthcare systems from the management of chronic diseases should recognise the value of interventions on lifestyle, including nutrition. These interventions provide opportunities for societal organisations, healthcare providers and food businesses to develop new technologies and products while using nutrition economic assessments to support their strategies. At present, a major issue is to build up expertise within the clinical community to run trials in nutrition-related matters to obtain evidence that can support decisions on interventions and that provide good value for money. Most investigators are used to a very restrictive phase III-type RCT, but policy evaluations are of a different nature. So far, we have fallen short of carrying out more pragmatic trials in many areas where these would generate the most useful data. The hard work that was done in the evaluation of medical technologies, set up conceptually from the late 1960s onwards and developed simultaneously in different places, in the absence of electronic communication, resulted only 30 years later in the creation of dedicated structures, organisations and networks, e.g. IQWIG (Institut für Qualität und Wirtschaftlichkeit im Gesundheidswesen), HAS (Haute Autorité de Santé), NICE (National Institute for Health and Clinical Excellence), INAHTA (International Network of Agencies for Health Technology Assessment), EuroScan, EUnetHTA (European Network for Health Technology Assessment), and so on. This was the time needed to build up sufficient examples of its application and to show that the methodology actually is a valuable aid in health policy

decision-making. The field of nutrition economics is now in a comparable situation of 'information gap period', and there is a need to start actively engaging key stakeholders to collect data, using measures that decision-makers will recognise. Within nutrition, some common metrics can be identified which allow us to judge the relative merits of clinically led interventions and public health advice. Then, as nutrition exemplifies all the types of interventions and policy which need evaluating across the health field, the demonstration that many nutritional issues have not been dealt with correctly in the current context will further enable us to enrich the basic outcome data and to develop more relevant approaches. This may then give insights into ways in which the overall HTA paradigm can be widened and thus contribute to broadening out the concept of the social welfare function beyond simple incremental cost-effectiveness ratios and application of qualitative judgements on equity, as happens in current decision-making. This may further lead to interactions with policies from other sectors which have health implications through the medium of nutrition such as agricultural policy, food pricing and taxation.

It is time to change the paradigm from the micro-level of evidence-based medicine to evidence-based decision-making, including meso- and macro-levels, and to convince health authorities that there should be a policy shift by introducing up-to-date knowledge of the importance of nutrition. The authors welcome any feedback and suggestions for further substantiating the value of nutrition interventions in the optimisation of public health.

REFERENCES

1 Park M, Braun T, Carrin G. (2007) Technical Briefs for Policymakers. WHO Department of Health Systems Financing No. 2. World Health Organization, Geneva.

2 Ginsburg PB. (2004) Controlling health care costs. *N Engl J Med*. 351, 1591–1593.

3 World Health Organization & European Observatory on Health Systems and Policies Series. (2005) Purchasing to Improve Health Systems Performance [J Figueras, R Robinson and E Jakubowski, editors]. Milton Keynes: Open University Press.

4 Drummond MF, Dubois D, Garattini L, *et al*. (1999) Current trends in the use of pharmacoeconomics and outcomes research in Europe. *Value Health* 2, 323–332.

5 Lenoir-Wijnkoop I, Dapoigny M, Dubois D, *et al*. (2011) Nutrition economics: characterising the economic and health impact of nutrition. *Br J Nutr*. 105, 157–166.

6 Fayers P, Bottomley A. (2002) Quality of life research within the EORTC – the EORTC QLQ-C30. *Eur J Cancer* 38, S125–S133.

7 Leidy NK, Revicki DA, Genesté B. (1999) Recommendations for evaluating the validity of quality of life claims for labeling and promotion. *Value Health* 2, 113–127.

8 FDA Guidance for Industry. (2009) Patient-reported outcome measures: use in medical product development to support labeling claims. www.fda.gov/downloads/Drugs/Guidance-ComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

9 Drummond M, Brixner D, Gold M, *et al*. (2009) Toward a consensus on the QALY. *Value Health* 12, S31–S35.

10 Cambridge, Harvard School of Public Health (1996) The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries and Risk Factors in 1990 and Projected to 2020 [CJL Murray and AD Lopez, editors]. Cambridge, MA: Harvard School of Public Health.

11 Torrance GW, Furlong W, Feeny D, *et al*. (1995) Multiattribute preference functions. Health Utilities Index. *Pharma-coeconomics* 7, 503–520.

12 Arnesen T, Trommald M. (2005) Are QALYs based on time-off comparable? A systematic review of TTO methodologies. *Health Econ*. 14, 39–53.

13 The EuroQol Group. (1990) EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 16, 199–208.

14 Richardson J, Iezzi A, Sihna K, *et al*. (2009) AQoL-7D (Vision)Instrument: Overview, survey results and utility algorithms. Monash University, Research Paper 2009 (45).

15 World Bank & World Development Report. (1993) Investing in Health. New York: Oxford University Press.

16 Soares MO (2012) Is the QALY blind, deaf and dumb to equity? NICE's considerations over equity. *Br Med Bull*. 101, 17–31.

17 Muldoon MF, Barger SD, Flory JD, *et al*. (1998) What are quality of life measurements measuring? *Br Med J*. 316, 542–545.

18 Slevin ML, Plant H, Lynch D, *et al*. (1988) Who should measure quality of life, the doctor or the patient? *Br J Cancer* 57, 109–112.

19 Measurement in clinical trials: review and qualification of clinical outcome assessments, Public Workshop October 2011, White Oak, MD. http://www.fda.gov/Drugs/NewsEvents/ucm276110.htm.

20 Fried TR, Tinetti ME, Towle V, *et al*. (2011) Effects of benefits and harms on older persons' willingness to take medication for primary cardiovascular prevention. *Arch Intern Med*. 171, 923–928.
21 Fidler C, Christensen TE, Gillard S. (2011) Hypoglycemia: an overview of fear of hypoglycemia, quality-of-life, and impact on costs. *J Med Econ*. 14, 646–655.
22 Nnoaham KE, Sacks G, Rayner M, *et al*. (2009) Modelling income group differences in the health and economic impacts of targeted food taxes and subsidies. *Int J Epidemiol*. 38, 1324–1333.
23 Duffey KJ, Gordon-Larsen P, Shikany JM, *et al*. (2010) Food price and diet and health outcomes: 20 years of The CARDIA Study. *Arch Intern Med*. 5, 420–426.
24 Observatory on Health Systems and Policies (2006) Health in All Policies – Prospects and Potentials [T Ståhl, M Wismar, E Ollila, *et al*. editors]. http://ec.europa.eu/health/archive/ph_information/documents/health_in_all_policies.pdf.
25 Ståhl T. (2010) Is health recognised in the EU's policy process? An analysis of the European Commission's impact assessments. *Eur J Public Health* 2, 176–181.
26 Ubel PA, Baron J, Nash B, *et al*. (2002) Are preferences for equity over efficiency in health care allocation "all or nothing"? *Med Care* 38, 366–373.
27 NICE (2011) Supporting local investment in public health – using evidence on cost effectiveness, cost impact and return on investment to inform local commissioning. http://www.nice.org.uk/media/737/C5/CostImpactSynopsis.pdf.
28 Graves N. (2006) Cost-effectiveness analyses and modelling the lifetime costs and benefits of health-behaviour interventions. *Chronic Illness* 2, 97–107.
29 Lenoir-Wijnkoop I, van Aalderen WM, Boehm G, *et al*. (2012) Cost-effectiveness model for a specific mixture of prebiotics in The Netherlands. *Eur J Health Econ*. 13, 101–110.
30 Lötters FJB, Lenoir-Wijnkoop I, Fardellone P, *et al*. (2012) Dairy foods and osteoporosis: an example of assessing the health-economic impact of food products. *Osteoporos Int*. 24(1):139-50. doi:10.1007/s00198-012-1998-6
31 Lotan Y, Buendia Jimenez I, Lenoir-Wijnkoop I*, et al*. (2012) Primary prevention of nephrolithiasis is cost-effective for a national health care system. Lotan Y, Buendia Jiménez I, Lenoir-Wijnkoop I, Daudon M, Molinier L, Tack I, Nuijten MJ. (2012) Primary prevention of nephrolithiasis is cost-effective for a national healthcare system. *BJU Int*. 110(11 Pt C):E1060-7.
32 Puska P, Nissinen A, Tuomilehto J. (1985) The community-based strategy to prevent coronary heart disease: conclusions from the ten years of the North Karelia project. *Ann Rev Public Health* 6, 147–193.
33 Puska P (2009) Fat and heart disease: yes we can make a change – the case of North Karelia (Finland). *Ann Nutr Metab*. 54, S33–S38.
34 Puska P, Ståhl T. (2010) Health in all policies – the Finnish initiative: background, principles, and current issues. *Annu Rev Public Health* 31, 315–328.
35 Sesé MA, Jimenez-Pavón D, Gilbert CC, *et al*. (2012) Eating behaviour, insulin resistance and cluster of metabolic risk factors in European adolescents. The HELENA Study. *Appetite* 59, 140–147.
36 Health Canada. (2006) Canadian Community Health Survey, Cycle 2.2, Nutrition (2004) – A Guide to Accessing and Interpreting the Data. Ottawa, ON: Health Canada. http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/surveill/cchs-guide-escc-eng.pdf.
37 Duffey KJ, Steffen LM, Van Horn L, *et al*. (2012) Dietary patterns matter: diet beverages and cardiometabolic risks in the longitudinal Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr*. 95, 909–915.

38 Buckland G, Agudo A, Luja'n L, *et al*. (2010) Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Am J Clin Nutr*. 91, 381–390.
39 Blumfield M, Hure A, MacDonald-Wicks L, *et al*. (2011) Disparities exist between national food group recommendations and the dietary intakes of women. *BMC Women's Health* 11, 37.
40 Upshur REG. (2003) Are all evidence-based practices alike? Problems in the ranking of evidence. *CMAJ* 169, 672–673.
41 Tonelli MR. (2001) The limits of evidence-based medicine. *Resp Care* 46, 1435–1440
42 Rothwell PM (2005) External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet* 365, 82–93.
43 Ioannidis JPA. (2008) Some main problems eroding the credibility and relevance of randomized trials. *Bull NYU Hosp Joint Dis*. 66, 135–139.
44 Guyatt GH, Oxman AD, Kunz R, *et al*. (2008) Rating quality of evidence and strength of recommendations: what is "quality of evidence" and why is it important to clinicians? *BMJ* 336, 995–998.
45 Rawlins M. (2008). De Testimonio: on the evidence for decisions about the use of therapeutic interventions. The Royal College of Physicians of London Harveian Oration. http://www.rcplondon.ac.uk/pubs/brochure.aspx?e=262
46 Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group (2004) Grading quality of evidence and strength of recommendations. *BMJ* 328, 1490.
47 Ibargoyen-Roteta N, Gutiérrez-Ibarluzea I, Rico-Iturrioz R, *et al*. (2010) The GRADE approach for assessing new technologies as applied to apheresis devices in ulcerative colitis. *Implement Sci.* 16, 48.
48 Nathan DM, Buse JB, Davidson MB, *et al*. (2006) Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 29, 1963–1972.
49 American Diabetes Association. (2008) Clinical practice recommendations. Standards of medical care in diabetes – 2008. *Diabetes Care* 31, Suppl. 1, S12–S54.
50 Agence Française de Sécurité Sanitaire des Produits de Santé. (2006) Traitement médicamenteux de l'ostéoporose post-ménopausique. Recommendations (Drug Treatment of Post-menopausal Osteoporosis. Recommendations). Saint-Denis: Agence Française de Sécurité Sanitaire des Produits de Santé.
51 Nuijten M, Renkens M, Kogels E, *et al*. (2011) The decision making process of payers: a pilot survey in The Netherlands. *ISPOR Connections* 8–9.
52 Plotnikoff GA. (2003) Food as medicine – cost-effective health care? *Minnesota Med*. 86, 41–45.
53 McCarron DA, Heaney RP. (2004) Estimated healthcare savings associated with adequate dairy food intake. *Am J Hypertens*. 17, 88–97.
54 Dalziel K, Segal L. (2007) Time to give nutrition interventions a higher profile: cost-effectiveness of 10 nutrition interventions. *Health Prom Int*. 22, 271–283.
55 Doidge JC, Gospodarevskaya E, Segal L. (2011) 7th Health Services & Policy Research Conference, Adelaide, SA, Australia.

Chapter 4

Cost-effectiveness model for a specific mixture of prebiotics in The Netherlands

Irene Lenoir-Wijnkoop, Wim M van Aalderen, Günther Boehm, Dineke Klaassen, Aline B Sprikkelman, Mark J Nuijten

Published in: Eur J Health Econ. 2012;13(1), 101-10

ABSTRACT

The objective of this study was to assess the cost-effectiveness of the use of prebiotics for the primary prevention of atopic dermatitis in The Netherlands. A model was constructed using decision analytical techniques. The model was developed to estimate the health economic impact of prebiotic preventive disease management of atopic dermatitis. Data sources used include published literature, clinical trials and official price/tariff lists and national population statistics. The comparator was no supplementation with prebiotics. The primary perspective for conducting the economic evaluation was based on the situation in The Netherlands in 2009. The results show that the use of prebiotics infant formula (IMMUNOFORTIS®) leads to an additional cost of €51 and an increase in Quality Adjusted Life Years (QALY) of 0.108, when compared with no prebiotics. Consequently, the use of infant formula with a specific mixture of prebiotics results in an incremental cost-effectiveness ratio (ICER) of €472. The sensitivity analyses show that the ICER remains in all analyses far below the threshold of €20,000/QALY.

Conclusion This study shows that the favourable health benefit of the use of a specific mixture of prebiotics results in positive short- and long-term health economic benefits. In addition, this study demonstrates that the use of infant formula with a specific mixture of prebiotics is a highly cost-effective way of preventing atopic dermatitis in The Netherlands.

BACKGROUND

Epidemiology

Atopic dermatitis (AD) is a chronic relapsing, inflammatory skin disease, characterized by a range of clinical features of which pruritus and typically distributed eczematous lesions are the most essential.[1-3] As the result of a two to threefold increase in prevalence during the last 3 decades, AD has become one of the most common childhood disorders.[3-5] A recent survey of Australian 13- to 14-year-olds, as part of the International Study of Asthma and Allergies in Childhood (ISAAC), found that the current prevalence of AD in that group was 10–12%.[6] Comparison of a birth cohort from 1965 to 1969, with one from 1975 to 1979 in Denmark, showed a doubling of the incidence of AD.[7] The incidence of AD in Great Britain increased from 5% in 1946 to 12.2% in 1970.[8]

Treatment of atopic dermatitis

Different treatments for AD have been investigated with varying results. Topical corticosteroids have been effective agents and the mainstay of treatment for many years. In the treatment of AD, a step-up approach is often used: from intermittent use of mild topical corticosteroid courses up to maintenance treatment with higher classes (more potent) topical corticosteroids.[9] When corticosteroids are not effective enough or are contraindicated, topical calcineurin inhibitors can be used as initial anti-inflammatory medication followed by a maintenance treatment.[9]

Quality of life

Atopic dermatitis patients are affected not only by the disease itself but also by the stigma associated with its visibility.[10,11] Chronic skin diseases have always had a major negative impact on a patient's quality of life (QoL), and since 1987, this impact can be measured in a repeatable standardized way.[12] Several questionnaires were developed to measure QoL in dermatology, e.g. the Dermatology Life Quality Index, the Children's Dermatology Life Quality Index and the Skindex-29.[13-15] Since then, the impairment of QoL and the psychological well-being of children with AD, as well as their parents, have been well documented.[16-25] A Dutch study by Brenninkmeijer *et al*. studied the impairment of quality of life and the psychological well-being of children with AD.[26] Patients with severe AD in childhood showed a significant delayed social development in their course of life. Very recently, several articles were published dealing with the development and use of a child-friendly version of EQ 5D.[27] However, there are no utility data available for children with AD collected by means of this child-friendly version of the EQ 5D.

Long-term co-morbidity

In later childhood, the prevalence of AD, food allergies and food allergen sensitization decreases, and the prevalence of asthma, allergic rhinitis and sensitization to inhalant allergens rises.[28,29] The term atopic march is commonly used to describe this typical progression from AD in young children to asthma at school age, not only in population studies but also in individual patients.[30,31] There is substantial ecological correlation between AD and asthma in the ISAAC Phase I.[6] An association between AD and asthma in childhood has been well documented,[6,32-34] and a similar association has been demonstrated in later life.[35] An association has also been demonstrated between AD and allergic rhinitis in childhood.[36,37] The onset of these conditions was frequently ordered with AD being the first in a triad of events that included asthma and allergic rhinitis. Underlying atopy is considered to be the thread that linked these disorders, and the term ''atopic march'' was developed to describe this sequential manifestation of atopy.[30,38]

Economic impact of atopic dermatitis

A systematic review carried out by Mancini et al.[39] of the socioeconomic effect of AD in the USA summarized four studies that contained good data on direct costs. They found a wide variation in estimated overall direct costs of AD in the USA, from US$364 million to US$3.8 billion per year. This large variation in estimates probably reflects the very different methods used in the various studies, and only one study measured indirect costs.

Preventive approaches of atopic dermatitis

Different intervention strategies have been tried to prevent AD in infants at risk, such as avoidance of trigger factors (e.g. heat, perspiration, house mite), treating skin infections (*staphylococcus aureus* and herpes simplex) and dietary measures including probiotics.[40-42] Studies by Moro and Arslanoglu explored the efficacy of a specific mixture of prebiotics in a clinical trial setting.[43,44] In a prospective, randomized, double-blind, placebo-controlled design, healthy term infants with a parental history of atopy were fed either a prebiotic-supplemented formula (8 g/L scGOS/lcFOS—IMMUNOFORTIS®) based on a mixture of neutral short-chain galactooligosaccharides (scGOS) and long-chain fructooligosaccharides (lcFOS) or placebo-supplemented (8 g/Lmaltodextrin) formula based on hydrolysed protein, during the first 6 months of life. Following this intervention period, blind follow-up continued until 2 years of life. Primary endpoints were cumulative incidence of allergic manifestations. Secondary endpoints were number of infectious episodes and growth. The mixture scGOS/lcFOS has been shown to reduce the incidence of AD and infectious episodes during the first 6 months of life. The results show a beneficial effect of prebiotics on the development of AD over a 6-month period in high-risk infants. The 6-months results were reported by Moro *et al*. and showed that 9.8% in the intervention group and 23.1% in the control group developed AD.[43] Arslanoglu *et al*. evaluated whether these preventive effects were lasting beyond the intervention period.[44] Cumulative

incidences for AD, recurrent wheezing and allergic urticaria were higher in the placebo group, (27.9, 20.6 and 10.3%, respectively) than in the intervention group (13.6, 7.6 and 1.5%; P<0.05).

OBJECTIVE

In the event that the favourable clinical benefits of a specific mixture of prebiotics may have an impact on cost-effectiveness, the objective of this study is to assess the cost-effectiveness of the use of prebiotics for the primary prevention of AD in The Netherlands.

METHODS

A model was constructed using decision analytical techniques.[45] The model was developed to estimate the health economic impact of prebiotic preventive disease management of AD. Data sources used include published literature, clinical trials and official price/tariff lists and national population statistics. This study was based on methodological guidance for cost-effectiveness studies in nutrition economics.[46]

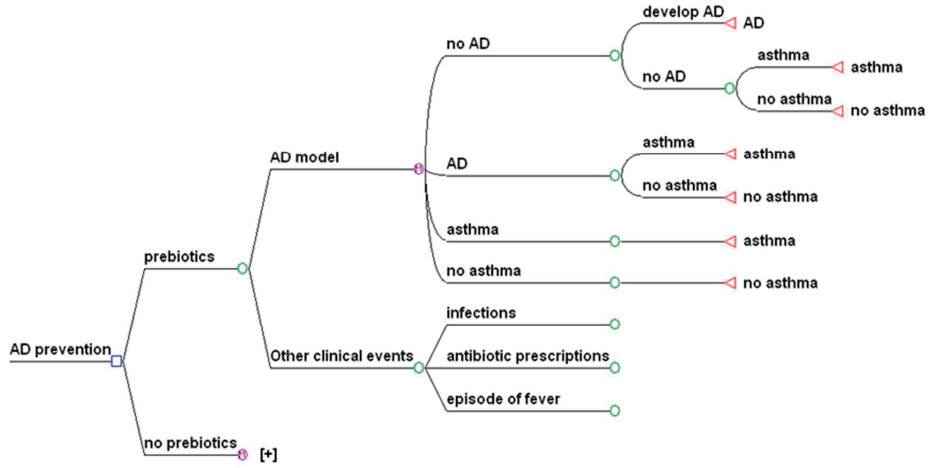
Model design

Decision analytical techniques are used to estimate the cost-effectiveness of the use of prebiotics for the primary prevention of AD, which is a well-accepted methodology and has been used in a number of published studies calculating the costs of medical strategies.[47] From treatment algorithms, a model can be constructed that considers the actions and their consequences over time. In effect, a model shows the consequences and complications of different therapeutic interventions, and it should correspond as much as possible to daily practice. Models may take the form of simple decision analytic trees or they may be complex Markov models. Whereas decision tree models are appropriate for acute episodes, Markov models are the first choice for cost-effectiveness analyses of short- and long-term consequences of transitions between multiple health states. The cost-effectiveness was calculated using a Markov model built in TreeAge Pro 2005/2006 reflecting treatment patterns and outcomes in management of AD. The Markov model was used to estimate the cost-effectiveness of the use of prebiotics for the primary prevention of AD, taking into account both the short- and long-term consequences of AD. Figure 1 shows the structure of the model. For this analysis, we defined four mutually exclusive health states:

- no atopic dermatitis
- atopic dermatitis
- no asthma
- asthma

Patient progression through these states was divided into cycles of 1 year. Infants may or may not develop AD. Among the children who develop AD, a significant proportion may develop long-term respiratory sequelae (e.g. asthma) after AD. The children without AD will have much lower probability of developing asthma based on population risk. The model also includes branches for a scenario analysis, which comprises the reduction in infections, reduced antibiotic prescriptions and reduced episodes of fever.

Figure 1. Structure of the model used in the analysis. (The base case model only includes the branches "atopic dermatitis" and "no atopic dermatitis"; the other branches are used in scenario analyses)



Study population

The model considers a cohort of children at risk for AD, in line with the populations as studied in the clinical trial assessing the efficacy of prebiotics for the primary prevention of AD over a period of 2 years. Healthy term infants with a parental history of AD, allergic rhinitis, or asthma in either mother or father were eligible for the clinical trial.[43,44] In all cases, the parental diagnosis was based on a documented physician's certification. Inclusion criteria were gestational age between 37 and 42 weeks, birth weight appropriate for gestational age and start of formula feeding within the first two weeks of life. Breast feeding was recommended to all mothers; the parents were informed about the study at discharge from the maternity unit and were asked to contact the hospital if they started formula feeding.

Comparison

The cost-effectiveness of prebiotic preventive disease management of AD is based on a comparison with no preventive intervention according to the Dutch guidelines for pharmacoeconomic research.[48]

Time horizon

Dutch guidelines for pharmacoeconomic research recommend analysis of long-term clinical effectiveness in order to evaluate healthcare technologies.[48] A reduction in the rate of AD was limited to 6-months prebiotics supplementation in the clinical trial, in which children were followed for 2 years from the point of randomization. Following the 6-months intervention period, blind follow-up continued until 2 years of life. The model assumes that the childhood asthma developing in AD infants will not persist beyond 16 years of age, which can be considered a conservative approach towards prebiotic preventive disease management of AD.

Thus, the base case analysis assumes a 16-year follow-up period starting at the beginning of the intervention in order to capture the impact of the use of prebiotics for the primary prevention of AD on long-term morbidity and mortality resulting from AD.

Setting and perspective

A primary care/outpatient setting is chosen for the evaluation, since most patients with AD and its sequelae are treated by general practitioners (GPs). The analysis is conducted from the perspective of the health insurance in The Netherlands in 2009, as not all relevant non-medical costs could be incorporated. As a consequence, the analysis can be considered conservative.

Clinical outcomes

The model extrapolated the efficacy data from the clinical trials (reduction in the rate of AD) to calculate the likely number of Quality Adjusted Life Years (QALYs) from the use of prebiotics. AD is associated with clinical and economic consequences beyond the clinical trial period. A proportion of the children may develop long-term sequelae (e.g. asthma) leading to a reduction in QALYs and additional medical costs. The analyses were based on a 16-year time horizon in order to capture long-term costs and morbidity beyond the AD episode, which include the medical costs for management of asthma.

Cost assessment

The cost assessment is based on:

- The costs for the use of infant formula with a specific mixture of prebiotics for the primary prevention of AD.
- The cost associated with treatment of sequelae and long-term morbidity (asthma).

The costs due to lost productivity are not included, as the model assumes that the childhood asthma associated with AD will not persist beyond 16 years.

Discounting and inflation

Future outcomes and costs are discounted at equal rates, when the time horizon of the model extends beyond a period of 1 year. Discounting is not applied within the base case analysis as the time horizon was less than 1 year. However, costs and benefits are discounted at a rate of, respectively, 4.0 and 1.5% per annum in sensitivity analyses using time horizons greater than 12 months. Finally, costs are updated to 2009 by applying an inflation correction.

DATA SOURCES

Probabilities

Atopic dermatitis

The probabilities are mainly based on efficacy measures from the clinical trial reports by Moro and Arslanoglu. The cumulative incidences for AD are 27.9 and 13.6% for, respectively, the placebo and the intervention group (Table 1).

Table 1. Probabilities from clinical trials

Moro[43] and Arslanoglu[44]	Probability (%) (cumulative over 2 years)		*P*-value
	Intervention	**Placebo**	
Atopic dermatitis	13.6	27.9	<0.05
Recurrent wheezing	7.6	20.6	<0.05
Allergic urticaria	1.5	10.3	<0.05
Infections (episodes)	1.8	2.7	<0.05

Asthma

The probability of the development of asthma was derived from the overview by Van der Hulst.[34] The pooled odds ratio for the risk of asthma after AD, compared with children without AD, in birth cohort studies was 2.14 (95% CI, 1.67–2.75). As the health economic model is based on probabilities, we used directly a probability of 0.20 (111/560) and 0.13 (335/2,543) for the development of asthma in, respectively, children with and without AD. However, in the RIVM report describing the ISAAC-II study and PIAMA study, it is reported that 4–7% of the children (0–12 years) has asthma in The Netherlands.[49] Therefore, the probability of the development of asthma in children either with or without AD may be based on an average of 5.5%. The OR is 4.3 based on probabilities of 0.20 and 0.055. Data for a scenario analysis were drawn from the Melbourne Atopic Cohort Study (MACS);[50] the investigators found that infants with atopic eczema (eczema plus sensitization) were at greater risk at ages 6 and 7 years of having childhood asthma (OR 3.52; 95% CI 1.88–6.59), allergic rhinitis (2.91; 1.48–5.71) and both childhood asthma and allergic rhinitis (6.30;

2.35–16.88) than infants with non-atopic eczema, even after excluding infants with early wheeze. The OR of 3.52 is for asthma only, which is lower than 4.3 based on the Dutch data. On the other hand, the OR is 6.30 for asthma and allergic rhinitis. However, allergic rhinitis will have a lower impact on costs and QALYs than asthma. Alternatively, the OR of 3.52 may be applied to the Dutch prevalence of 0.055 in the normal population in order to calculate the probability of asthma after AD (0.17).

The base case analysis is based on data from the review by Van der Hulst: 0.20 (AD) and 0.13 (no AD) risk of development of asthma. As indicated above, a scenario analysis is based on the OR (3.52) from the Melbourne Atopic Cohort Study, which was applied to an average of 5.5% prevalence of asthma according to RIVM data: 0.17 (AD) and 0.055 (no AD) risk of development of asthma. The children will only develop asthma from 6 years of onset, which was based on the finding from the Melbourne Atopic Cohort Study (Table 2).

Table 2. Risk of asthma

Sources	Probability (%)		*P*-value	OR
	AD	**No AD**		
Van der Hulst[34]	20	13	<0.05	2.14
Van der Hulst[34]/RIVM[49]	20	5.5 (4-7)	NA	4.3
MACS[50]	Asthma			3.52
	Asthma + allergic rhinitis			6.30
MACS/RIVM	0.17	0.055		

Utilities

Atopic dermatitis

A study by Poole *et al*. provided utilities for the model.[51] This study showed that patients with AD of all severities presented considerable decrements in health-related utility. Although this utility study was performed in adults, the utilities were included in the model. There is no evidence that utilities for children may be different from those for adults. Although the psychological impact of visible eczema may not be relevant for small children, the physiological impact in this population may be worse than in adults. A sensitivity analysis was performed on the utilities to capture any uncertainty in our assumptions. In the study by Poole *et al*., utilities are reported for mild, moderate and severe AD. The health economic model is based on the utilities of the EQ-5D questionnaire, which is the most accepted utility scale. The utilities are mild—0.848, moderate—0.796 and severe—0.760. This study shows that patients with AD will experience a utility of 0.027 improvement following treatment. In our model, we therefore used the following utility values: mild—0.875 (0.848+0.027), moderate—0.823

(0.796+0.027) and severe—0.787 (0.760+0.027). The distribution in the study by Poole was 28.7% mild, 36.0% moderate and 35.3% severe. A weighted average utility (0.825) was used in our model based on the distribution of mild, moderate and severe.

Asthma

A study by Greenough *et al*. reported utilities in children with a history of RSV infection using the Health Utility Index (HUI), a multi-attribute score that includes measures for sensation, mobility, emotion, cognition, self-care, pain, vision, hearing, speech, ambulation and dexterity.[52] Investigations of the long-term prognosis of patients with severe RSV disease in infancy have shown measurable respiratory abnormalities, such as asthma and recurrent wheezing, which may persist for several years following infection.[53,54] These long-term respiratory abnormalities are comparable for children developing AD. Therefore, we used the utilities from the study of Greenough *et al*.[52] In the analysis, it was assumed that high-risk children who did not experience asthma following AD would have a utility corresponding with a median HUI 2 for non-RSV-infected children (u=0.95); high-risk children who experienced asthma following AD would have a utility corresponding with a median HUI 2 for RSV-infected children (u=0.88); all children above 16 years of age and all children without AD would have perfect health (u= 1; Table 3).

Table 3. Utilities of asthma

	Utility		Source
	No treatment	**Treatment**	
			Poole[51]
Mild AD	0.848	0.875	
Moderate AD	0.796	0.823	
Severe AD	0.760	0.787	
No AD	1.00	1.00	
			Greenough [52]
Asthma	<16 years		
Asthma after AD	0.88		
No asthma after AD	0.95		

Use of prebiotics

The cost of a 6-months period consumption of infant formula with a specific mixture of prebiotics is €325, which is based on the average consumer price in The Netherlands, Italy and Germany and total dosage of 19,500 g. The model is based on the 6-months period in the trial by Moro and Arslanoglu, and therefore, cost of a 6-months period prebiotics consumption was used. The 6-months cost of no preventive approach was €250.

Other medical costs

Medication

In the treatment of AD, a step-up approach is used often: patients receive mild topical corticosteroid courses of variable duration and no subsequent maintenance therapy to speak of.[9] The costs of corticosteroids are minimal and are therefore excluded from the model, as prescribing patterns are not available in the literature. This is a conservative assumption for the model, especially because more expensive medication may also be considered (e.g. topical calcineurin).

Consultations

There are no Dutch data available on the cost of treatment of AD. The study by Su provides annual consultations for treatment of AD.[55] Although costing information is country-specific, we used these data as starting point for a validation by Dutch clinical experts (Table 4). The base case analysis is based on GP consultations only, which was considered a conservative approach by the Dutch clinical experts.

Table 4. Medical consultations per year as reported in study by Su[55]

Type of consultation	Degree of eczema		
	Mild	**Moderate**	**Severe**
General practitioner	4.0	7.0	11.7
Paediatrician	0.5	2.8	1.6
Allergist	0.2	0.3	3.3
Dermatologist	2.7	3.2	6.4

The costs were incorporated in the model for a period of 2 years. We assume that this is the average duration of AD. The cost of a GP is €20.20 and of a specialist is €50.00 for non-academic and €100.00 for academic hospital, which are used in the current health economic model after inflation correction for 2009. A sensitivity analysis is based on the inclusion of a specialist visit varying from lower to upper limit.

Costs of long-term morbidity

A recent report presents information on healthcare use and costs related to asthma and chronic obstructive pulmonary disease (COPD) in The Netherlands.[56] Total costs for treating asthma in 2000 were estimated to be €141 million. Annual costs per patient in the 0–14 age group came to approximately €233, which is used in the current health economic model after inflation correction to 2009.

RESULTS

The base case analysis does only include AD, and other clinical events are not included. The use of infant formula with a specific mixture of prebiotics leads to an additional cost of €51 and an increase in QALYs of 0.108, when compared with no prebiotic supplementation (Table 5).

Consequently, the use of infant formula with prebiotics results in an ICER of €472/QALY. The informal threshold in The Netherlands is €20,000/QALY, and therefore, the use of infant formula with prebiotics can be considered very cost-effective with only an ICER of €472/QALY.

Table 5 shows also the results for an analysis based on the OR from the Melbourne Atopic Cohort Study, which was applied to an average of 5.5% prevalence of asthma according to RIVM data. The use of prebiotics results in an ICER of €325/QALY, which is slightly lower than the ICER in the base case analysis (€472/QALY). A sensitivity analysis was based on the cost of consultation. The assumption in the base case is that all consultations for treatment of AD are by a GP. A sensitivity analysis is based on cost of specialist (non-academic hospital and academic hospital tariffs as indicated above). The ICER changes from €472 to €439 and €393 (Table 5). A sensitivity analysis was based on the assumption that infant formula with a specific mixture of prebiotics is used for a full year: the ICER decreases from €472 to €398.

A sensitivity analysis was based on the assumption that AD has no impact on utility of a child. Therefore, utility value for AD was 1 in this sensitivity analysis: the ICER increases from €472 to €615 (Table 5).

Finally, a scenario analysis was performed, which includes the costs of treatment of the other clinical events: recurrent wheezing, allergic urticaria, infection and fever. The assumption is that each side effect leads to one extra GP visit. This analysis shows a cost saving of €467 per patient (Table 5). The use of prebiotics is considered dominant over ‘‘no prebiotics’’: cost savings and a higher effectiveness. Overall, the sensitivity analyses show that ICER remains in all analyses far below the threshold of €20,000/QALY.

Table 5. Results

	Prebiotics	No prebiotics	Diff.
Base case			
Costs	€622	€571	€51
QALYs	14.108	14.000	0.108
ICER-QALY	€472		
No discounting			
Costs	€760	€719	€41
QALYs	15.716	15.598	0.118
ICER-QALY	€348		
OR Melbourne			
Costs	€476	€438	€38
QALYs	14.184	14.067	0.117
ICER-QALY	€325		
Cost specialist (non academic)			
Costs	€626	€579	€47
QALYs	14.108	14.000	0.108
ICER-QALY	€439		
Cost specialist (academic)			
Costs	€632	€590	€42
QALYs	14.108	14.000	0.108
ICER-QALY	€393		
Full year prebiotics			
Costs	€797	€754	€43
QALYs	14.108	14.000	0.108
ICER-QALY	€398		
Utility AD = 1 (base case 0.825)			
Costs	€622	€571	€51
QALYs	14.132	14.049	0.083
ICER-QALY	€615		
Including other clinical events			
Costs	€897	€1,364	- €467
QALYs	14.108	14.000	0.108
ICER-QALY	Dom.		

DISCUSSION

This economic evaluation demonstrates that the supplementation of infant formula with a specific mixture of prebiotics is a highly cost-effective approach for prevention of AD, costing €472/QALY gained relative to ''no prebiotics''. This ICER is well below the ''threshold'' range of €20,000 per QALY. Extensive sensitivity analyses indicate that the conclusions are extremely robust, remaining unaltered despite significant changes in key model parameters.

The results of any modelling exercise need to be treated with some degree of caution. Decision analytic techniques, upon which our model is based, have several weaknesses. Various data sources were used for the model, which all have their pros and cons from a clinical and health economic perspective. Among the general model limitations is the fact that clinical trial data do not necessarily represent real clinical practice. Data from clinical trials do not necessarily have a high degree of external validity as the results are often contingent upon protocol adherence, a situation that may not be easily replicated outside the trial setting. Therefore, we applied a scenario analysis, which was based on a different underlying source: the Melbourne Atopic Cohort Study.[50] The analysis showed that the use of prebiotics results in an ICER of €325/QALY, which is in line with the ICER in the base case analysis (€472/QALY).

A review of the literature shows that AD can be a major disorder with significant costs and morbidity. An Australian study of the impact on families of the care of a child with AD found that looking after a child with moderate or severe AD was significantly more stressful than looking after a child with insulin-dependent diabetes mellitus.[55]

There are many reasons for the impact of AD on the family. Disturbed sleep is a significant factor that may contribute to both child and parental morbidity. For children with severe eczema, the average number of hours sleep lost by parents per night averaged 1.9h, and the parental estimate of loss of childhood sleep was 2.1h per night. These Australian findings are comparable to the 2.6h of parental sleep lost per night reported by a recent English study.[57] Care of a child with AD can interfere significantly with other activities. Thus, the time spent treating children per day was of the order of 1.5–3h. Parental employment was reduced, ceased or not started for 40% of parents looking after children in the moderate or severe eczema groups, in the recent Australian study. Direct costs include cost of medications, dressings, special diet and out-of-pocket costs for professional consultations. Income loss for parental time off work was also estimated. A study by Kemp showed that the costs of care per year vary from AU$1,142 yearly for mild eczema, to AU$6,099 for severe allergic eczema.[58]

Based on this overview, we can conclude that our model was based on a number of conservative assumptions, as all costs and morbidities of AD reported in the previous section were not included in the model. Indirect costs due to working days lost for the parents for AD and asthma were not included. Other non-medical costs, like transportation costs to the hospital, due to AD and asthma were also not included in the model. Studies indicate that episodes with asthma in children may lead to a significant number of days lost from school, interference with physical exercise and under-functioning at school because of interrupted sleep.[59] In cases of more severe asthma, the more frequent school absences may affect the individual's education and, possibly, choice of career. In addition to the extensive individual burden of asthma, the burden on the family is substantial. Additional housework may be required to reduce the child's exposure to potential environmental triggers. Time ''off work'' may be required to take care of a sick child. The costs of treatment of the other clinical events: recurrent wheezing, allergic urticaria, infection and fever were not included in the base case analysis and only included in a sensitivity analysis. The model assumes that the childhood asthma developing after AD will not persist beyond 16 years of age, which can be considered as a conservative approach towards disease management of AD, as many children will also suffer from asthma as adults. Summarizing, this analysis can be considered conservative from a societal perspective, as not all relevant costs could be incorporated. The inclusion of non-medical costs would have resulted in more cost savings by prebiotics in the primary prevention of AD and therefore even a lower ICER in terms of Cost per QALY than the current analysis from a health insurance perspective. Given that there are some limitations to the modelling technique, its advantages should also be pointed out. The ideal design to demonstrate the possible long-term health economic outcomes associated with prebiotics would be a naturalistic prospective study, which may require a follow-up period varying from 10 to 20 years. The use of a Markov model allowed us to extrapolate clinical outcomes beyond the duration of the existing clinical trials. Sensitivity analyses confirmed the robustness of the model.

Finally, there are also potential cost savings at a national level, as shown by the scenario analysis, which includes the other clinical events. The cost savings per child are €467, which may result in a substantial positive impact on the budget. The incidence of AD in children was estimated at 5% in Spain and 20% in England. Dutch data from national statistics show a total of 181,000 babies born in 2007.[60] Thus, the number of at-risk babies varies between 9,050 and 36,200. The total annual national cost saving may be at least €4.2 million, when saving €467 in 9,050 babies.

CONCLUSION

This study shows that the favourable health benefit of the use of infant formula with a specific mixture of prebiotics results in positive short- and long-term health economic benefits. Furthermore, this study demonstrates that the use of infant formula with a specific mixture of prebiotics (IMMUNOFORTIS®) is a highly cost-effective approach for the prevention of atopic dermatitis in The Netherlands. This may also lead to substantial cost savings at a national level, when all clinical events are included.

REFERENCES

1 Leung DY, Bieber T. (2003) Atopic dermatitis. *Lancet* 361, 151–160.

2 Kunz B., Oranje AP, Labreze L, *et al*. (1997) Clinical validation and guidelines for the SCORAD index: consensus report of the European task force on atopic dermatitis. *Dermatology* 195, 10–19.

3 Sturgill S., Bernard LA. (2004) Atopic dermatitis update. *Curr Opin Pediatr*. 16, 396–401.

4 Levy RM, Gelfand JM, Yan AC. (2003) The epidemiology of atopic dermatitis. *Clin Dermatol*. 21, 109–115.

5 Williams HC. (2000) Epidemiology of atopic dermatitis. *Clin Exp Dermatol*. 25, 522–529.

6 The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. (1998) Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema. *Lancet* 351, 1225–1232.

7 Schultz-Larsen F. (1993) Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol*. 28, 719–723.

8 Butland B, Strachan DP, Lewis S, Bynner J, Butler N, Britton J. (1997) Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. *BMJ* 315, 717–721.

9 Reitamo S, Remitz A, Haahtela T. (2009) Hit early and hit hard in atopic dermatitis and not only in asthma. *Allergy* 64, 503–504.

10 Carroll CL, Balkrishnan R, Feldman SR, *et al*. (2005) The burden of atopic dermatitis: impact on the patient, family, and society. *Pediatr Dermatol*. 22, 192–199.

11 Schmid-Ott G, Kuensebeck HW, Jaeger B, *et al*. (1999) Validity study for the stigmatization experience in atopic dermatitis and psoriatic patients. *Acta Derm Venereol*. 79, 443–447.

12 Ben-Gashir MA. (2003) Relationship between quality of life and disease severity in atopic dermatitis/eczema syndrome during childhood. *Curr Opin Allergy Clin Immunol*. 3, 369–373.

13 Finlay AY, Khan GK. (1994): Dermatology life quality index (DLQI)–a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 19, 210–216.

14 Lewis-Jones MS, Finlay AY. (1995) The children's dermatology life quality index (CDLQI): initial validation and practical use. *Br J Dermatol*. 32, 942–949.

15 Abeni D, Picardi A, Pasquini P, *et al*. (2002) Further evidence of the validity and reliability of the Skindex-29: an Italian study on 2,242 dermatological outpatients. *Dermatology* 204, 43–49.

16 Absolon CM, Cottrell D, Eldridge SM, *et al*. (1997) Psychological disturbance in atopic eczema: the extent of the problem in schoolaged children. *Br J Dermatol*. 137, 241–245.

17 Beattie PE, Lewis-Jones MS. (2006) A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol*. 155, 145–151.

18 Ben-Gashir MA, Seed P, Hay RJ. (2004) Quality of life and disease severity are correlated in children with atopic dermatitis. *Br J Dermatol*. 150, 284–290.

19 Chamlin SL, Cella D, Frieden IJ, *et al*. (2005) Development of the childhood atopic dermatitis impact scale: initial validation of a quality-of-life measure for young children with atopic dermatitis and their families. *J Invest Dermatol*. 125, 1106–1111.

20 Holm EA, Wulf HC, Stegmann H, *et al*. (2006) Life quality assessment among patients with atopic eczema. *Br J Dermatol*. 154, 719–725.

21 Kiebert G, Sorensen SV, Revicki D, *et al*. (2002) Atopic dermatitis is associated with a decrement in health-related quality of life. *Int J Dermatol*. 41, 151–158.

22 Lewis-Jones S. (2005) Measuring the burden of atopic eczema in young children and the family unit. *J Invest Dermatol*. 125, viii.
23 Lundberg L, Johannesson M, Silverdahl M, *et al*. (2000) Health related quality of life in patients with psoriasis and atopic dermatitis measured with SF-36, DLQI and a subjective measure of disease activity. *Acta Derm Venereol*. 80, 430–434.
24 Sampogna F, Picardi A, Chren MM, *et al*. (2004) Association between poorer quality of life and psychiatric morbidity in patients with different dermatological conditions. *Psychosom Med*. 66, 620–624.
25 Wittkowski A, Richards HL, Griffiths CE, *et al*. (2004) The impact of psychological and clinical factors on quality of life in individuals with atopic dermatitis. *J Psychosom Res*. 57, 195–200.
26 Brenninkmeijer EEA, Legierse CM, Sillevis Smitt JH, Last BF, Grootenhuis MA, Bos JD. (2009) The course of life of patients with childhood atopic dermatitis. *Allergy* 64, 840–848.
27 Wille N, Badia X, Bonsel G, Burström K, Cavrini G, Devlin N, Egmar AC, Greiner W, Gusi N, Herdman M, Jelsma J, Kind P, Scalone L, Ravens-Sieberer U. (2010) Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res*. 19(6), 875–886.
28 Rhodes HL. (2001) Early life risk factors for adult asthma: a birth cohort study of subjects at risk. *J. Allergy Clin Immunol*. 108, 720–725.
29 Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U, *et al*. (1999) Natural course of sensitization to food and inhalant allergens during the first 6 years of life. J. *Allergy Clin Immunol*. 103, 1173–1179.
30 Spergel JH, Paller AS. (2003) Atopic dermatitis and the atopic march. *J Allergy Clin Immunol*. 112, S118–S127.
31 Liu AH, Martinez FD, Taussig LM. (2003) Natural history of allergic diseases and asthma. In: Leung DYM, Sampson HA, Geha RS, Szefler SJ. (eds.) Pediatric Allergy: Principles and Practice, pp. 10–22. Elsevier, Philadelphia.
32 Bergmann RL, Edenharter G, Bergmann KE, Forster J, *et al*. (1998) Atopic dermatitis in early infancy predicts allergic airway disease at 5 years. *Clin Exp Allergy* 28, 965–970.
33 Gustafsson D. Sjoberg O, Foucard T. (2000) Development of allergies and asthma in infants and young children with atopic dermatitis— a prospective follow-up to 7 years of age. *Allergy* 55, 240–245.
34 Van der Hulst AE, Klip H, Brand PL. (2007) Risk of developing asthma in young children with atopic eczema: a systematic review. *J Allergy Clin Immunol*. 120, 565–569.
35 Hanifin JM, Reed ML. (2007) A population-based survey of eczema prevalence in the United States. *Dermatitis* 18, 82–91.
36 Martin Fernandez-Mayoralas D, Martin Caballero JM, Garcia-Marcos Alvare, L. (2004) Association between atopic dermatitis, allergic rhinitis and asthma in schoolchildren aged 13–14 years old. *An Pediatr. (Barc)* 60, 236–242.
37 Hakansson K, Thomsen SF, Ulrik CS, Porsbjerg C, *et al*. (2007) Increase in the prevalence of rhinitis among Danish children from 1986 to 2001. *Pediatr Allergy Immunol*. 18, 154–159.
38 Simpson EL, Hanifin JM. (2005) Atopic dermatitis. *J Am Acad Dermatol*. 53, 115–128.
39 Mancini AJ, Kaulback K, Chamlin SL. (2008) The socioeconomic impact of atopic dermatitis in the United States: a systematic review. *Pediatr Dermatol*. 25, 1–6.
40 Kalliomäki M, Salminen S. Poussa T, Arvilommi H, Isolauri E. (2003) Probiotics and prevention of atopic disease: 4-year follow-up of a randomized placebo-controlled trial. *Lancet* 361, 1869–1871.

41 Kalliomäki M, Salminen S, Poussa T, Isolauri E. (2007) Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo-controlled trial. *J. Allergy Clin Immunol*. 119, 1019–1021.
42 Wickens K, Black PN, Stanley TV, Mitchell E, *et al*. (2008) A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. *J. Allergy Clin Immunol*. 122, 788–794.
43 Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. (2006) A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Arch Dis Child*. 91, 814–819.
44 Arslanoglu S, Moro G, Schmitt J, Tandoi L, Rizzardi S, Boehm G. (2008) Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *J Nutr*. 138, 1091–1095.
45 Weinstein MC, Fineberg HV. (1980) Clinical Decision Analysis, pp. 228–265. WB Saunders Co, Philadelphia, PA.
46 Lenoir-Wijnkoop I, Dapoigny M, Dubois Dvan Ganse E, Gutiérrez-Ibarluzea I, Hutton J, Jones P, Mittendorf T, Poley MJ, Salminen S, Nuijten MJ. (2010) Nutrition economics— characterising the economic and health impact of nutrition. *Br J Nutr*. 1–9. doi:10.1017/s0007114510003041
47 Nuijten MJC, Al M, Rutten F. (2003) In search for more confidence in health economic modelling (thesis)
48 Richtlijnen voor farmaco-economisch onderzoek. Geactualiseerde versie (April 2006). College voor zorgverzekeringen. Diemen. Maart 2006.
49 RIVM. www.rivm.nl/vtv/object_document/o4663n18082.html.
50 Lowe AJ, Abramson MJ, Hosking CS, Carlin JB, *et al*. (2007) The temporal sequence of allergic sensitization and onset of infantile eczema. *Clin Exp Allergy* 37, 536–542.
51 Poole D, Chambers C, Sidhu MK, Currie CJ. (2009) Health-related utility among adults with atopic dermatitis treated with tacrolimus ointment as maintenance therapy over the long term: findings from the Protopic_CONTROL study. *Br. Dermatol*. 161, 1335–1340.
52 Greenough A, Alexander J, Burgess S, Bytham J, Chetcuti PA, Hagan J, Lenney W, Melville S, Shaw NJ, Boorman J, Coles S, Turner J, Pang F. (2004) Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection. *Arch Dis Child*. 89(7), 673–678.
53 Malhotra A, Krilov LR. (2000) Influenza and respiratory syncytial virus. Update on infection, management and prevention. *Pediatr Clin North Am*. 47, 353–372.
54 Welliver R, Duffy L. (1993) The relationship of RSV-specific immunoglobulin E antibody responses in infancy, recurrent wheezing and pulmonary functions at age 7–8 years. *Pediatr Pulmonol*. 15, 19–27.
55 Su JC, Kemp AS, Varigos GA, Nolan TM. (1997) Atopic eczema: its impact on the family and financial cost. *Arch Dis Child*. 76, 159–162.
56 Hoogendoorn EJI, Feenstra TL, Rutten-van Mölken MPMH.(2004) Inventarisatie van het gebruik en de kosten van zorg voor astma en COPD in Nederland. RIVM rapport 260604001.
57 Reid P, Lewis-Jones MS. (1995) Sleep difficulties and their management in preschoolers with atopic eczema. *Clin Exp Dermatol*. 20, 38–41.
58 Kemp AS. (1999) Atopic eczema: its social and financial costs. *J. Paediatr. Child Health* 35, 229–231.
59 Lenny W. (1997) The burden of pediatric asthma. *Pediatr. Pulmonol. Suppl*. 15, 13–16.
60 http://www.cbs.nl/nl-NL/menu/themas/bevolking/cijfers/extra/piramide-fx.htm.

Chapter 5

Nutrition economics – food as an ally of public health

Irene Lenoir-Wijnkoop, Peter J Jones, Ricardo Uauy, Leonie Segal, John Milner

Published in: Br J Nutr. 2013;109(5), 777-84

ABSTRACT

Non-communicable diseases (NCD) are a major and increasing contributor to morbidity and mortality in developed and developing countries. Much of the chronic disease burden is preventable through modification of lifestyle behaviours, and increased attention is being focused on identifying and implementing effective preventative health strategies. Nutrition has been identified as a major modifiable determinant of NCD. The recent merging of health economics and nutritional sciences to form the nascent discipline of nutrition economics aims to assess the impact of diet on health and disease prevention, and to evaluate options for changing dietary choices, while incorporating an understanding of the immediate impacts and downstream consequences. In short, nutrition economics allows for generation of policy-relevant evidence, and as such the discipline is a crucial partner in achieving better population nutritional status and improvements in public health and wellness. The objective of the present paper is to summarise presentations made at a satellite symposium held during the 11th European Nutrition Conference, 28 October 2011, where the role of nutrition and its potential to reduce the public health burden through alleviating undernutrition and nutrition deficiencies, promoting better-quality diets and incorporating a role for functional foods were discussed.

BACKGROUND

Nutrition economics represents an emerging sub-branch of health economics. The term was introduced in early 2011 by a group of multidisciplinary specialists who defined it as 'a discipline dedicated to researching and characterizing health and economic outcomes in nutrition for the benefit of society'.[1] Nutrition is undoubtedly a major modifiable determinant of disease. At the recent United Nations general assembly on non-communicable disease (NCD) prevention and control, held in September 2011, the importance of establishing preventative health strategies was widely acknowledged. Such acknowledgement reflects the widening evidence base, which now suggests that if the major risk factors for chronic disease were eliminated, around three-quarters of heart disease, stroke and type 2 diabetes would be prevented along with 40% of cancers. Furthermore, nine million people die prematurely, often before the age of 60 years, from NCD. Over 90% of these premature deaths due to NCD occur in developing countries.[2] Meanwhile, health care expenditure continues to rise faster than economic growth in most high-income countries;[3] in the past 10 years, health care expenditures in countries of the Organisation for Economic Cooperation and Development have increased by 50%. Nutrition economics thus plays a core role in establishing preventative health strategies through food and in the prioritisation of interventional measures, both of which optimize the health and wellbeing of society. Nutrition economics is relevant in all countries and applies to policies concerning fortified, conventional and functional food entities. The tasks of nutrition economics are first to assess the impact of diet on health and disease prevention, expressed in policy-relevant terms, and second to evaluate options for changing dietary choices, including regulatory measures, social marketing, differential pricing, direct service provision and negotiations with industry. Economic evaluation determines the relative efficiency of alternative investment strategies for enhancing wellbeing, and, in the context of nutrition economics, can be employed to ensure that scarce resources are allocated more efficiently to reduce the burden of harm from inadequate-quality diets. A methodological approach for the measurement of health outcomes in nutrition may be considered depending on a three-point continuum of efficacy, effectiveness and efficiency.[1] Efficacy is a standard measure used in randomised controlled trials to determine whether an intervention works under controlled conditions. The outcomes have high internal validity, but often low external validity, and may not be easily generalised. A treatment may be efficacious in randomised controlled trials, but if the treatment is not used in the correct way by people in their everyday life, then the intervention will not have effectiveness. Thus, effectiveness refers to whether an intervention works under real daily life circumstances, without the rigorous compliance conditions applied in efficacy trials. Efficiency adds cost considerations to the latter by asking the question 'is it worth it?'. Value may be defined as the real health outcome per

unit of financial investment. The aim of the present paper is to discuss the role of nutrition and its impact in reducing the public health burden through (i) alleviating undernutrition and micronutrient deficiencies, (ii) promoting healthy choice of conventional foods and (iii) enhancing the use of functional foods for health improvement and disease risk reduction. A further goal is to improve awareness among health professionals, authorities and decision makers and to look at long-term sustainable approaches to enhance health, including the adoption of nutritional strategies. Attaining this goal may require reorganisation of healthcare expenditure models to generate policy-relevant evidence for the implementation of initiatives.

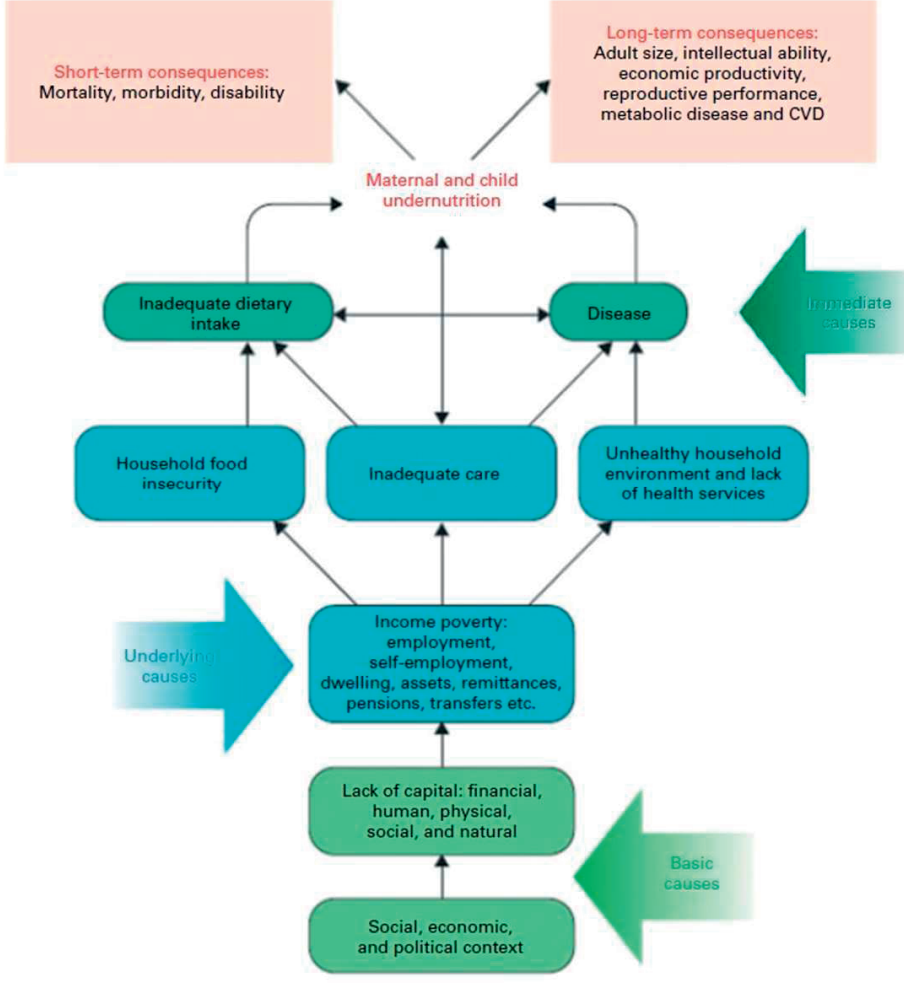
THE ECONOMIC BURDEN OF UNDERNUTRITION

The commitment by governments to eradicate hunger and undernutrition is not only an ethical imperative, but also a sound investment that will yield significant economic gains and major social benefits. Investment in nutrition in early life will benefit not only the present generation, but also their children as well as subsequent generations. Data on the economic costs of undernutrition help to inform the policy decision-making process. It is important to consider the effects of undernutrition in terms of both its impact on short- and long-term outcomes. Early nutrition defines to a great extent how many people will survive infancy and what quality of life they can expect up until death. Undernutrition and infection in childhood are major determinants of a short life expectancy, while physical activity and diet have greater influence on the causes of morbidity and mortality among ageing populations. Among the leading risk factors for morbidity worldwide, high blood pressure is a major contributor to mortality in both developed and developing countries alike, while tobacco use increasingly influences morbidity in developing countries.[4] Nutrient deficiencies, such as Fe, I, Zn and vitamin A, still have an important effect on mortality and disability-adjusted life years among children aged under 5 years in developing countries.[5]

While significant gains in life expectancy have been observed in many countries over the last 50 years, a loss in life expectancy has been observed in eight countries of sub-Saharan Africa and in North Korea.[6] A net gain in healthy life years has been demonstrated from the beginning to the end of the twentieth century among American males by an elevation in the age of onset of some chronic conditions, including heart disease, arthritis, neoplasm and respiratory conditions of 7–10 years.[7] Indeed, prevention of morbidity and mortality is demonstrated to have a direct effect on economic growth. In India, half of the recent economic growth may be accounted for by the increasing survival and prevention of disability among the adult population, leading to enhanced productivity in older age. An

investment in increasing adult survival rate by 1% in developing countries is linked to a 0·05% increase in gross domestic product growth rate, while a similar increase of 1% in investment: gross domestic product ratio is associated with a 0·014% increase in growth rate.[8] It is now recognised that early undernutrition has consequences not only in the short term for morbidity, disability and death, but also in the long term for intellectual ability, economic productivity, reproductive performance, diabetes and CVD (Figure 1).[5] The link between the timing of investment in human capital and loss of functionality after reaching adulthood has been investigated, showing that the greatest benefit can be achieved from an investment during the initial 1000 days of life (*i.e.* from the time before conception to the end of the second postnatal year of life) for physical and mental development.

Figure. 1. Maternal and child undernutrition and its short-term and long-term consequences[5]



What we fail to do in that time period cannot be recovered; for example, iodine deficiency in early life may lead to a loss of 40–50 IQ points in developmental tests, which cannot be improved upon afterwards. Conversely, the present model shows that in fact the greatest investment is made in the last 1000 days of life, and the level of investment here is far greater than that made in the early years of life.[9,10]

Stunting is the most common form of undernutrition. At the present time, stunting affects around 178 million children, mainly in Africa and Asia, and to a lesser extent in Latin America.[5] Stunting may be avoided by having an appropriate birth weight and appropriate nutrition over the first years of life; it is almost impossible to reverse stunting after the third year of life. Deviation from the norm in height at the age of 2 years is associated with differences in height at adulthood attained in the analysis of five cohorts from developing countries.[11] Not only is linear growth negatively affected in the early years, but also brain and muscle growth become restricted, which is important in terms of labour, productivity and work output, IQ, as well as mental development. Many countries have targeted school feeding programmes based on low body weight rather than weight for height indices. Foods distributed in such programmes are high-energy/high-protein foods but are often not fortified with adequate micronutrients, resulting in very limited gain in weight and no gain in body length. One of the problems in providing food to undernourished children is that while weight and fat gains may be achieved, less progress is made in terms of length for age, suggesting a trend towards making children heavier and possibly promoting obesity.[12] A better approach would be to target undernutrition during the prenatal period and early years of life.

The consequences of linear growth retardation are multiple. Growth retardation can lead to a higher risk of death in childhood, lower scores in developmental tests (IQ) and in school performance, with higher rates of drop outs and a decrease in lean body mass, which affects physical work capacity. Higher risks of labour complications in women and retarded fetal growth have also been observed. The latter suggests a trans-generational effect of undernutrition in which the effects are passed from the mother to the next generation. The impact of growth retardation is exemplified by a cohort of pregnant Guatemalan women identified in 1975 whose children had been followed up to the age of 35 years.[13] Children who were stunted at 3 years of age ended up being 12 cm shorter than the control group in the same population. Children with severe stunting tended to have 0·6 years less schooling than the control group, so the educational achievement was also less. In adult life, the mean income of this population was 26000 Quetzales for men and 8000 Quetzales for women, while the severely stunted population had a significantly lower income, at over 3000 Quetzales less among men and 1800 Quetzales less than average among women.[13] This finding suggests that we may be spending

money at the wrong time and that a greater investment should be made in early life to maximise productivity, health and wellbeing in adulthood. The Economic Commission for Latin America and the Caribbean has conducted an evaluation of the economic costs of undernutrition, finding that the economic losses for thirteen countries across the region due to undernutrition amount to US$17 billion or 3·4% of gross national product on average.[14] Only 8% of the losses due to undernutrition can be accounted for by poor health and reduction in school attendance at a young age, while lost productivity throughout adult life due to poor educational performance and poor linear growth accounts for as much as 92% of the loss.

A high proportion of the NCD burden in China can be traced back to nutrition in early life.[15] Stunting was associated with nearly 10% of cases of CHD, 11% of strokes and 34% of type 2 diabetes among the population in 1995. For mortality, in 1995, diet-related NCD were responsible for 2·5 million deaths (or 43% of all deaths), over 1 million cancer deaths, 1·1 million stroke deaths and 350 000 deaths due to CHD. The economic cost of diet-related NCD in China was estimated at 2·4% of gross domestic product in 1995.

Prioritising steps to address undernutrition

In the context of limited resources and competing needs, economic impact evaluations contribute to providing valuable information that enables decisions on how to spend effectively and efficaciously, for the greatest benefit relative to money spent. Economic evaluation is a systematic and transparent framework for assessing benefits; it is used to help make decisions and does not make decisions directly. Methodological challenges and uncertainties associated with nutrition interventions to improve health of the next generation, including aspects such as affordability, equity, ethical concerns and political feasibility, need to be addressed. Evaluation of economic impact to prioritise possible steps is both desirable and an inevitable constraint. Economist members of the Copenhagen Consensus panel ranked top priorities for global health measures, taking into account the economic costs and benefits of different measures. In 2004, projects with a good rating for the ability to effect change included two measures to address undernutrition through providing micronutrients and the development of new agricultural technologies, while improving infant and child nutrition and reducing the prevalence of low birth weight were given a fair rating. In the 2008 consensus, steps to address undernutrition were given a higher priority, with five nutritional interventions appearing in the top ten health priorities, including micronutrient supplementation for children (vitamin A and Zn) and micronutrient fortification (Fe and salt iodisation), biofortification of crops, nutrition programmes at school and community-based nutrition promotion.

ECONOMICS OF NUTRITION: ITS ROLE IN EVIDENCE-POLICY TRANSLATION

The three main roles of economics in relation to nutrition are: (i) establishing the cost or burden of disease, that is, defining how big the problem is or how important nutrition is in health and well-being; (ii) economic evaluation, to define which services to expand by comparing the performance across different nutrition interventions and between nutrition and other modalities for improving health; and lastly (iii) establishing how best to achieve the desired change in nutritional behaviour.

Cost of illness/burden of disease

In estimating the burden of poor nutrition, published studies build part of the case for developing and implementing effective interventions. Studies in this area aim to assess the morbidity and mortality attributable to poor diet in terms of years of life lost, disability-adjusted life years lost, deaths and/or quality-adjusted life years (QALY) lost, as well as expenditure on treatment of nutrition-related conditions. The impact on total economic output or indirect costs can also be measured, estimating how nutrition-related diseases affect workforce participation and productivity. Developing these estimates requires good-quality data on the relative risk of disease attributable to alternative foods or whole diet patterns and of present food consumption patterns. Nonetheless, from the limited published studies, poor diets can be demonstrated to have major implications on the burden of disease. For example, the cost of low dairy consumption on health of Australians has been calculated in a systematic analysis.[16] An initial literature review collated the best published evidence on the relative risk of low *vs.* high consumption of dairy products on health, and described the causal pathways between dairy products and disease. A causal link between low dairy product consumption and incidence of disease/risk factors has been established for osteoporosis, obesity, hypertension, IHD, stroke and type 2 diabetes.[17–21] The greatest influence of low dairy product consumption was on the incidence of obesity, based primarily on evidence from the Coronary Artery Risk Development in Young Adults study.[20,21]

The population attributable risk (PAR) is the percentage of the disease/condition that is attributable to the particular risk, in this case low dairy product intake. PAR is based on relative risk, consumption patterns and other risk factors that influence disease incidence. In determining total burden, the existence of overlapping causal pathways needs to be adjusted for. For example, obesity is a known risk factor for hypertension, IHD, stroke and type 2 diabetes, and needs to be taken into consideration when assessing the burden of low dairy product consumption to avoid double counting. The recommended daily dairy product consumption in Australia is two to three servings

(the level at which disease risk is minimised), but 65% of the population fail to regularly meet these recommendations for dairy product consumption.[22] Estimation of PAR for the Australian population suggests that 18% of cases of obesity could be attributed to low dairy product consumption, and so were 10% of type 2 diabetes, 16% of stroke, 8% of hypertension and 6% of osteoporosis cases. These values also represent the best estimates of disease that could be avoided by adopting the recommended daily servings of dairy products (Table 1).[16] For osteoporosis, the percentage of disease found to be attributable to low dairy product consumption seems low; however, there is a serious lack of quality studies of dairy product consumption and incidence of osteoporosis on which to base these calculations. The PAR may be applied to the burden of disease estimates for each disease type to estimate total burden of disease in terms of health expenditure and morbidity/mortality attributable to low dairy product consumption. PAR applied to published data on the costs of healthcare expenditure associated with each of the six illnesses/risk factors provides estimates for the total health expenditure attributable to low dairy consumption.

Table 1. Direct healthcare expenditure and burden of disease attributable to low consumption of dairy products in Australia, 2010–11[16]

	Costs of illness attributable to low consumption of dairy products										
	Base case analysis					Sensitivity analysis S1			Sensitivity analysis S2		
		$million		DALY			$million	DALY		$million	DALY
Disease or risk factor	PAR (%)	Sep†	Σ‡	Sep†	Σ‡	PAR (%)	Σ‡	Σ‡	PAR (%)	Σ‡	Σ‡
Obesity	18·4	1468	1076	54 754	8365	10·1	588	4574	29·8§	1741	13 536
T2DM	10·2	503	237	46 208	18 342	5·1	119	9233	13·0‖	304	23 465
IHD	5·0	122	122	13 638	13 638	2·5	61	6862	14·3¶	347	38 867
Stroke	16·2	238	238	21 873	21 873	8·2	120	11 015	26·4¶	388	35 641
Hypertension	8·3	173	112	17 148	10 794	4·3	58	5608	25·6**	345	33 130
Osteoporosis	6·2	223	223	2000	2000	3·1	112	1006	19·9††	716	6423
Total			2007		75 012		1059	38 299		3839	151 061

DALY, disability-adjusted life year; PAR, population attributable risk; Sep, separately; T2DM, type 2 diabetes mellitus.
*Values are point estimates.
†Application of the PAR to the corresponding estimate of individual direct healthcare expenditure or burden of disease.
‡Application of the PAR to the corresponding estimate of combined direct healthcare expenditure or burden of disease.
§ Based on combination of data for Australian population and data reported in Pereira *et al*.[20]
‖ Based on data reported in Choi *et al*.[36]
¶ Based on data reported in van der Pols *et al*.[37]
**Based on data reported in Alonso *et al*.[38]
††Based on data reported in Jaglal *et al*.[39]

After adjusting to avoid double counting, health expenditure in Australia attributable to low dairy product consumption for the six disease areas has surged to over AU$2000 million.[16] This amount is approaching the total public health budget in Australia of AU$2265 million. In addition, a substantial total burden in terms of 75 000 disability-adjusted life years was found to be attributable to low dairy product consumption. This research serves to demonstrate the impact that compromised nutrition can have

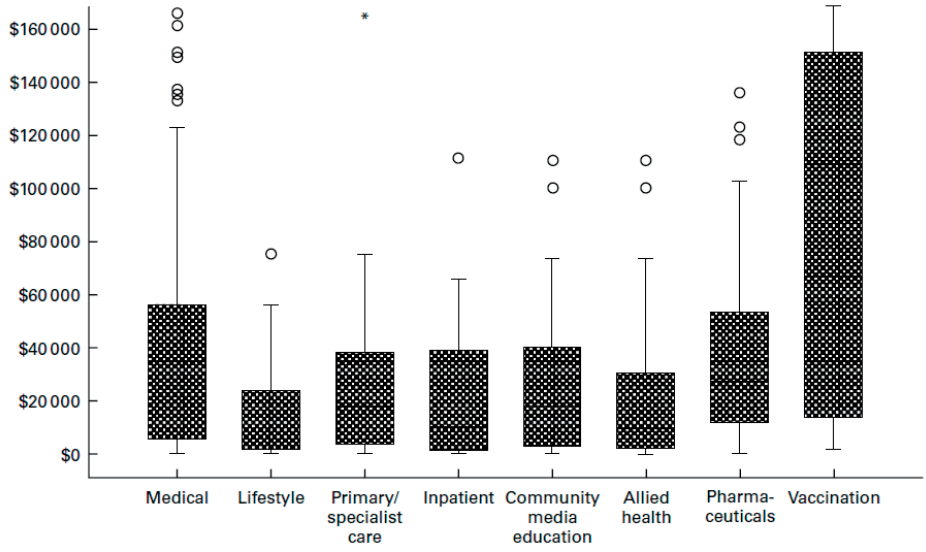
on burden of disease and the potential value of identifying effective and cost-effective approaches to improving diet.

Economic evaluation

Economic evaluation is used to evaluate the benefits and costs of a single intervention, or compare the costs and consequences of two or more alternatives in order to best enable resource allocation choices. Economic evaluation typically seeks to express inputs and outputs in monetary terms, in order to calculate a net present value, or return on investment (value of benefits relative to value of costs) of the future stream of benefits and costs, known as a cost–benefit analysis. Health economics more often takes the form of cost–utility analysis, where performance is measured in terms of the cost of achieving a QALY gain, or cost-effectiveness analysis, where performance is expressed as the cost of achieving a predetermined clinical outcome or event. All health economic evaluations need to draw upon the best available clinical evidence. A cost–utility analysis of a Mediterranean diet after an acute myocardial infarction illustrates the use of economic evaluation.

In a controlled trial, 605 patients post-acute myocardial infarction were randomised to either a Mediterranean diet or a low-fat diet recommended by the American Heart Association.[23] A number of clinical events, including death, were gathered up to 5 years post-intervention. Key dietary changes were observed among the Mediterranean diet group, including lower consumption of processed and fresh meat and butter/cream, and a higher consumption of bread, legumes, vegetables, fruits and rapeseed oil margarine. These dietary improvements were associated with between 65 and 72% reduction in all-cause mortality, major cardiovascular events and stroke over the 5-year follow-up among those receiving the Mediterranean diet compared with those on the American Heart Association diet. Cost per QALY gain for the Mediterranean diet was estimated at AU$1013 (US$703, €579)[24] and the QALY gain per person was estimated at 0·4.[25] These gains compare most favourably with the cost–utility analysis of other nutrition interventions.[25] For example, for the prevention of type 2 diabetes, the cost per QALY gain upon adoption of a reduced fat diet among persons with impaired glucose tolerance was estimated to be AU$10 000, with only a small benefit of 0·024 QALY gain per person, while adoption of an intensive lifestyle among persons with impaired glucose tolerance had greater benefit at a cost–utility of AU$1880, with a QALY gain per person of 0·41.[25] A study of 245 health interventions has reported that lifestyle changes and allied health interventions, which include nutrition intervention, are considerably more cost-effective on average than medical interventions, pharmaceuticals or vaccination (Figure 2).[26]

Figure 2. Box plot: incremental cost-effectiveness ratios for published Australian cost-effectiveness studies of 245 health interventions[26]



Policy translation

Nutrition economics is crucial for the generation of policy-relevant evidence and informed policy decision making to enhance nutrition choices. But does evidence of cost-effectiveness influence policy and practice? From the aforementioned Australian study of 245 health interventions, it was found that cost-effectiveness results do have some influence, notably on what is not funded, tending to exclude services that perform most poorly. However, cost-effectiveness was not found to influence the level of funding, *i.e*. the likelihood that those in the target group would gain access to funded services. Rather, the major influence on the level of funding and access was found to be funding models. In many countries, including Australia, funding models favour medical and pharmaceutical interventions at the expense of lifestyle and nutrition interventions.[27] This means that specific steps need to be taken to allow the accumulating cost-effectiveness evidence for nutrition interventions to influence policy and practice. Appropriate policy responses should aim to assist citizens to make well-informed nutrition choices. Promoting knowledge of healthy and unhealthy food choices through food labelling and evidence-based social marketing campaigns, taxation of unhealthy foods, subsidising of healthy food choices and restriction of junk food advertising are just a few examples of steps that may be taken to promote healthy nutrition choices. Thus, nutrition economics is a crucial partner in the achievement of better nutrition at the population level. It is the discipline for translating evidence on what constitutes

a healthy diet into policy, to achieve desired change in patient/consumer/provider/industry behaviours.

HEALTH IMPROVEMENT THROUGH (FUNCTIONAL) FOOD

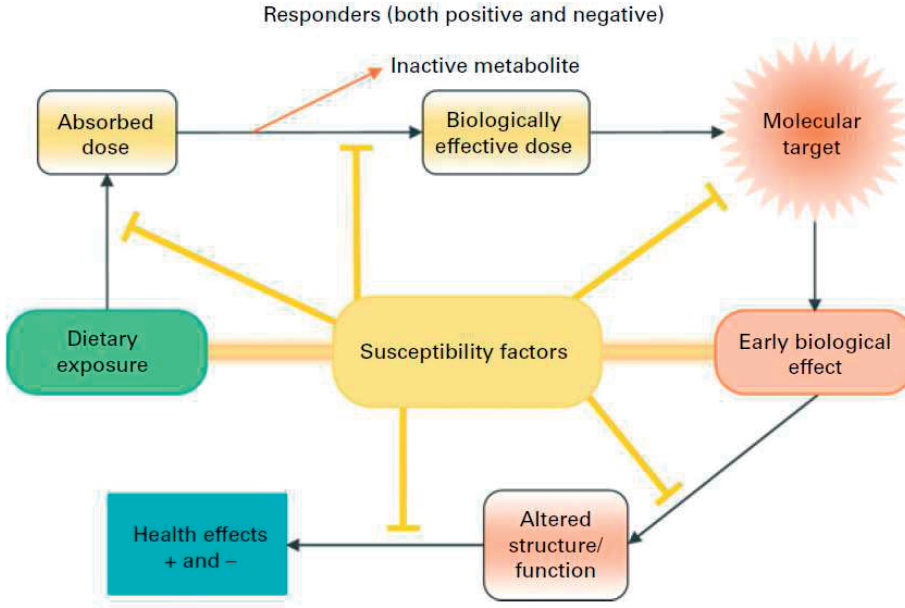
The WHO definition of health is 'a state of complete physical, mental and social well-being and not merely the absence of disease and infirmity'. The world is changing, with cancer predicted to be the leading cause of death through to 2030.[28] Society is ageing and more mutations occur as we get older. Diet plays a critical role in the prevention of ill health: cancers can be caused either by inadequacy of nutrients or overindulgence and half of cancers occur in developing countries. Premature death due to NCD is a significant issue that has a huge impact on productivity, and has recently been discussed by the United Nations General Assembly in September 2011. Cancer, diabetes, heart disease and lung disease kill 36 million people worldwide every year, making up 63% of global deaths.[29] Prevention strategies involving dietary and lifestyle changes have been proposed to address this global health problem.[29] However, this is not a new concept, as over 2500 years ago Hippocrates recognised that a balance of healthy diet and physical activity was required to achieve and maintain positive health. The societal and economic benefits of adoption of a healthy lifestyle may be enormous. A WHO report of the Southeast Asia region suggested that at least 80% of cases of premature heart disease, stroke and type 2 diabetes and 40% of cancers could be prevented through lifestyle changes, including a healthy diet, regular physical exercise and avoiding tobacco products. Furthermore, in the Southeast Asia region, a 2% annual reduction in deaths due to chronic disease was shown to be capable of saving over 8 million lives in the next 10 years, of which over 5 million people would be aged 70 years.[30] In India alone, a similar reduction would also result in an economic gain of US$15 billion over the next 10 years. A recent cost analysis from Harvard University suggests that unless present health trends are reversed, the five common NCD – cancer, diabetes, heart disease, lung disease and mental health problems – will cost the world US$47 trillion in treatment costs and lost wages over the next 20 years.[31]

Biomarkers for evaluating inter-individual variation in response

Inter-individual variation in the response to food and its components is commonplace. For example, in a study examining the effect of increased olive oil consumption on lowering LDL-cholesterol level, only 25–30% of people responded in the predicted way with a lower LDL-cholesterol level, 10% of people had the opposite response and around 60% of people failed to respond at all.[32] Red meat is associated with an increased cancer risk across a number of studies; a meta-analysis has shown an approximately

20% increased risk of colorectal cancer associated with red meat consumption more than five times per week.[33] A French population study has identified a subpopulation of around 4% with polymorphisms in the cytochrome P450 genes, who have almost a 50-fold increased risk of colorectal cancer from red meat intake when consumed over five times per week.[34] This finding suggests that models for cost-effectiveness may need to consider nutrigenomics and phenotypes, and determination of the cost-effectiveness of many interventions needs to target the population at risk and not the general population.

Figure 3. The three types of biomarkers needed to determine response to foods/components (source: J Milner, unpublished results)



To adequately determine response to food and components, three types of biomarkers need to be considered, including dietary exposure, susceptibility factors and early biological effect (Figure 3). What kind of exposure is required and how much need to be determined, as does the kind of desired biological effect. Susceptibility biomarkers may consider how genetic differences influence biological responses.

In the past, general population nutritional campaigns have achieved limited success in terms of positive education regarding food and nutrition. In the future, the food industry paradigm shift from considering the cost of food to modifying foods to give value-added benefits should be considered in terms of health promotion from early life. What is the cost associated with adding nutrients to bring intake up to recommended levels? The

economic impact of meeting 2010 federal dietary guidelines for Americans to consume more K, dietary fibre, vitamin D, Ca and to get less energy from saturated fat and added sugar has been examined for the adult population of King County, Washington.[35] Increasing the consumption of K, the most expensive of the four recommended nutrients, was predicted to add US$380 per year to the average consumer's food costs; meanwhile, each time consumers obtained 1% more of their daily energy from saturated fat and added sugar, their food costs significantly declined. Thus, improving diet will require additional guidance for consumers, especially those with little budget flexibility, and new policies to increase the availability and reduce the cost of healthy foods.

In summary, what is the best way to communicate the so-called four Ps for public health promotion: predictive, personalised, pre-emptive and participatory? While biomarkers may be used to accurately predict when adequate levels of nutrients are reached, a personalised approach will account for inter-subject variability in response, pre-emptive timing, e.g. preconception will optimise response and the joint participation of scientists in academia, governments and industry will ensure the best outcome.

CONCLUSION

The emerging field of nutrition economics aims to assess the impact of diet and health on disease prevention and to characterise the health and economic aspects of specific changes in nutritional behaviour and nutrition recommendations. In the present paper, the importance of translating the influence of nutrition on health and its impact in reducing the public health burden has been illustrated from three different perspectives, *i.e*. alleviating undernutrition and nutrient deficiencies, enhancing conventional foods and offering selected (functional) foods. There is a need to improve awareness among health authorities and decision makers of the very considerable benefits of better-quality diets and of the effective and cost-effective policies that can achieve that goal. Nutrition economics has a major role in informing this desirable policy direction.

REFERENCES

1 Lenoir-Wijnkoop I, Dapoigny M, Dubois D, *et al*. (2011) Nutrition economics – characterising the economic and health impact of nutrition. *Br J Nutr.* 105, 157–166.

2 WHO (2011) Ten facts on non-communicable diseases. http://www.who.int/features/factfiles/noncommunicable_diseases/en/index.html

3 Watson R. (2006) Health spending rising faster than GDP in most rich countries. *BMJ* 333, 60.

4 WHO (2009) Global health risks: mortality and burden of disease attributable to selected major risks. http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf

5 Black RE, Allen LH, Bhutta ZA, *et al*. (2008) Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 371, 243–260.

6 McMichael AJ, McKee M, Shkolnikov V, *et al*. (2004) Mortality trends and setbacks: global convergence or divergence? *Lancet* 363, 1155–1159.

7 Vogel RW. (2003) Changes in the process of aging during the twentieth century: findings and procedures of the early indicators project. Working Paper 9941. http://www.nber.org/papers/w9941

8 Bhargava A, Jamison DT, Lau L, *et al*. (2001) Modelling the effects of health on economic growth. *J Health Econ* 20, 423–440.

9 Forget EL, Roos LL, Deber RB, *et al*. (2008) Variations in life-time healthcare costs across a population. *Healthc Policy* 4, e148–e167.

10 Dormont B, Oliveira Martins J, Pelgrin F, *et al*. (2008) Health expenditures, longevity and growth. http://dx.doi.org/10.2139/ssrn.1130315

11 Victora CG, Adair L, Fall C, *et al*. for the Maternal and Child Undernutrition Study Group (2008) Maternal and child undernutrition: consequences for adult health and human capital. *Lancet* 371, 340–357.

12 Uauy R, Albala C, Kain J. (2001) Obesity trends in Latin America: transiting from under- to overweight. *J Nutr* 131, 893S–899S.

13 Hoddinott J, Maluccio JA, Behrman JR, *et al*. (2008) Effect of a nutrition intervention during early childhood on economic productivity in Guatemalan adults. *Lancet* 371, 411–416.

14 Martínez R, Fernández A. (2008) The cost of hunger: social and economic impact of child undernutrition in Central America and the Dominican Republic. Economic Commission for Latin America and the Caribbean (ECLAC). http://www.cepal.org/publicaciones/xml/9/32669/DP_CostHunger.pdf

15 Popkin BM, Horton S, Kim S, *et al*. (2001) Trends in diet, nutritional status, and diet-related noncommunicable diseases in China and India: the economic costs of the nutrition transition. *Nutr Rev*. 59, 379–390.

16 Doidge JC, Gospodarevskaya E, Segal L. (2012) Attributable risk analysis reveals potential healthcare savings from increased consumption of dairy products. *J Nutr*. 142, 1772–1780.

17 Cumming RG, Nevitt MC (1997) Calcium for prevention of osteoporotic fractures in postmenopausal women. *J Bone Miner Res*. 12, 1321–1329.

18 Ralston RA, Lee JH, Truby H, *et al*. (2012) A systematic review and meta-analysis of elevated blood pressure and consumption of dairy foods. *J Hum Hypertens*. 26, 3–13.

19 Elwood PC, Pickering JE, Givens DI, *et al*. (2010) The consumption of milk and dairy foods and the incidence of vascular disease and diabetes: an overview of the evidence. *Lipids* 45, 925–939.

20 Pereira MA, Jacobs DR, Van Horn L, *et al*. (2002) Dairy consumption, obesity, and the insulin resistance syndrome in young adults. *JAMA* 287, 2081–2089.

21 Dougkas A, Reynolds CK, Givens ID, *et al*. (2011) Associations between dairy consumption and body weight: a review of the evidence and underlying mechanisms. *Nutr Res Rev*. 15, 1–24.
22 Doidge JC, Segal L (2012) Most Australians do not meet recommendations for dairy consumption: findings of a new technique to analyse nutrition surveys. *Aust N Z J Public Health* 36, 236–240.
23 de Lorgeril M, Salen P, Martin JL, *et al*. (1999) Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 99, 779–785.
24 Dalziel K, Segal L, de Lorgeril M (2006) A Mediterranean diet is cost-effective in patients with previous myocardial infarction. *J Nutr*. 136, 1879–1885.
25 Dalziel K, Segal L. (2007) Time to give nutrition interventions a higher profile: cost-effectiveness of 10 nutrition interventions. *Health Promot Int*. 22, 271–283.
26 Dalziel K, Segal L, Mortimer D. (2008) Review of Australian health economic evaluation – 245 interventions: what can we say about cost effectiveness? *Cost Eff Resour Alloc*. 6, 9.
27 Segal L, Dalziel K, Mortimer D. (2010) Fixing the game: are between-silo differences in funding arrangements handicapping some interventions and giving others a head-start? *Health Econ*. 19, 449–465.
28 Mathers CD, Loncar D (2005) Updated projections of global mortality and burden of disease, 2002–2030: data sources, methods and results. http://www.who.int/healthinfo/statistics/bodprojectionspaper.pdf
29 WHO (2010) Global status report on noncommunicable diseases. http://whqlibdoc.who.int/publications/2011/9789240686458_eng.pdf
30 WHO (2005) Facing the facts: the impact of chronic disease in South-East Asia. http://www.who.int/chp/chronic_disease_report/media/searo.pdf
31 Bloom DE, Cafiero ET, Jané-Llopis E, *et al*. (2011) The Global Economic Burden of Noncommunicable Diseases. Geneva: World Economic Forum. http://www.weforum.org/reports/global-economic-burden-non-communicable-diseases
32 Kris-Etherton PM, Derr J, Mitchell DC, *et al*. (1993) The role of fatty acid saturation on plasma lipids, lipoproteins, and apolipoproteins: I. Effects of whole food diets high in cocoa butter, olive oil, soybean oil, dairy butter, and milk chocolate on the plasma lipids of young men. *Metabolism* 42, 121–129.
33 Larsson SC, Wolk A. (2006) Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer* 119, 2657–2664.
34 Küry S, Buecher B, Robiou-du-Pont S, *et al*. (2007) Combinations of cytochrome P450 gene polymorphisms enhancing the risk for sporadic colorectal cancer related to red meat consumption. *Cancer Epidemiol Biomarkers Prev*. 16, 1460–1467.
35 Monsivais P, Aggarwal A, Drewnowski A .(2011) Following federal guidelines to increase nutrient consumption may lead to higher food costs for consumers. *Health Aff. (Millwood)* 30, 1471–1477.
36 Choi HK, Willett WC, Stampfer MF, *et al*. (2005) Dairy consumption and risk of type 2 diabetes mellitus in men: a prospective study. *Arch Intern Med*. 165, 997–1003.
37 van der Pols JC, Gunnell D, Williams GM, *et al*. (2009) Childhood dairy and calcium intake and cardiovascular mortality in adulthood: 65-year follow-up of the Boyd Orr cohort. *Heart* 95, 1600–1606.
38 Alonso A, Beunza JJ, Delgado-Rodríguez M, *et al*. (2005) Low-fat dairy consumption and reduced risk of hypertension: the Seguimiento Universidad de Navarra (SUN) cohort. *Am J Clin Nutr.* 82, 972–979.

39 Jaglal SB, Kreiger N, Darlington G. (1993) Past and recent physical activity and risk of hip fracture. *Am J Epidemiol.* 138, 107–118.

Chapter 6

Dairy foods and osteoporosis: an example of assessing the health-economic impact of food products

Freek JB Lötters, Irene Lenoir-Wijnkoop, Patrice Fardellone, René Rizzoli, Emilie Rocher, Marten J Poley

Published in: Osteoporos Int. 2013;24(1), 139-50

ABSTRACT

Summary Osteoporosis has become a major health concern, carrying a substantial burden in terms of health outcomes and costs. We constructed a model to quantify the potential effect of an additional intake of calcium from dairy foods on the risk of osteoporotic fracture, taking a health economics perspective.

Introduction This study seeks, first, to estimate the impact of an increased dairy consumption on reducing the burden of osteoporosis in terms of health outcomes and costs, and, second, to contribute to a generic methodology for assessing the health-economic outcomes of food products. We constructed a model that generated the number of hip fractures that potentially can be prevented with dairy foods intakes, and then calculated costs avoided, considering the healthcare costs of hip fractures and the costs of additional dairy foods, as well as the number of disability-adjusted life years (DALYs) lost due to hip fractures associated with low nutritional calcium intake. Separate analyses were done for The Netherlands, France, and Sweden, three countries with different levels of dairy products consumption.

Results The number of hip fractures that may potentially be prevented each year with additional dairy products was highest in France (2,023), followed by Sweden (455) and The Netherlands (132). The yearly number of DALYs lost was 6,263 for France, 1,246 for Sweden, and 374 for The Netherlands. The corresponding total costs that might potentially be avoided are about €129 million, €34 million, and €6 million, in these countries, respectively.

Conclusion This study quantified the potential nutrition economic impact of increased dairy consumption on osteoporotic fractures, building connections between the fields of nutrition and health economics. Future research should further collect longitudinal population data for documenting the net benefits of increasing dairy consumption on bone health and on the related utilization of healthcare resources.

INTRODUCTION

Health benefits of dairy foods, which provide a large variety of essential nutrients such as minerals, vitamins, and proteins, are widely recognized.[1] Dairy foods, consumed by many people throughout the Western world as part of the daily diet,[2,3] are a determinant of human health and wellbeing. Although the extent of those effects has not been completely unfolded, some of the reported benefits concern the area of cardiovascular diseases, colorectal cancer, obesity and type 2 diabetes.[4-6] Several studies have documented the link between the intake of dairy foods and osteoporosis, associating low dietary calcium intake with decreased bone density and osteoporotic fractures, as dairy products consistently provide 60 % to 70 % of daily calcium intakes.[7-12] In a review by McCarron and Heaney on the effects of dairy products in several medical conditions, they concluded that in the USA intake of the recommended quantities of dairy products would yield 5-year savings (limited to healthcare costs) of $209 billion. Of this, $14 billion relate to savings on the healthcare costs for osteoporosis (limited to treating fractures).[13] Over the past decades, osteoporosis has become a major health concern, estimated to affect over 200 million people worldwide.[14,15] The disease carries a substantial burden. First, osteoporosis increases the risk of fractures, associated with increased mortality, increased morbidity, limitations in physical function, pain, and losses in health-related quality of life.[16,17] Second, osteoporotic fractures considerably increase healthcare costs, in both inpatient and outpatient settings, as has been confirmed by several studies.[18-20] Calcium and vitamin D supplementation, anti-osteoporotic drugs, and exercise programs have been shown to be effective in reducing the risk of fractures.[21,22] However, in daily practice non-compliance appears to be a significant problem with specific anti-osteoporotic therapy and with calcium and vitamin D supplementation as well.[23,24] This provides a rationale for supporting a more food-oriented preventive approach of osteoporosis. The purpose of this study was to explore the relationship between a food-related health condition and its potential impact on health care expenditures. Currently, the literature contains hardly any relevant studies on the impact of dairy foods on healthcare costs or cost-effectiveness.[25,26]

Despite the fact that the effects of foods on health are increasingly recognized, there is no accepted, proven methodology to assess the health-economic impact of foods in the general population. The scarcity of estimations on the health-economic impact of foods stands in sharp contrast with the ever-growing evidence on the cost-effectiveness of (public) health technologies.[27,28] Obviously, the evidence most adapted to a general population setting as well to the long latency periods for nutrition-related diseases mainly has to come from prospective cohort studies with disease events and death as outcome.

In this paper, we propose an approach for estimating the potential nutrition economic impact of dairy products on the burden of osteoporosis in the general population over 50 years of age. The aims are first, to quantify the burden of osteoporosis (in terms of costs and health outcomes) and to estimate the potential impact of increasing dairy foods consumption on reducing this burden. These calculations were performed for France, The Netherlands, and Sweden. Secondly, this study aims to contribute to the development of a generic methodology for assessing the health-economic outcomes of food products.

MATERIALS AND METHODS

Data sources

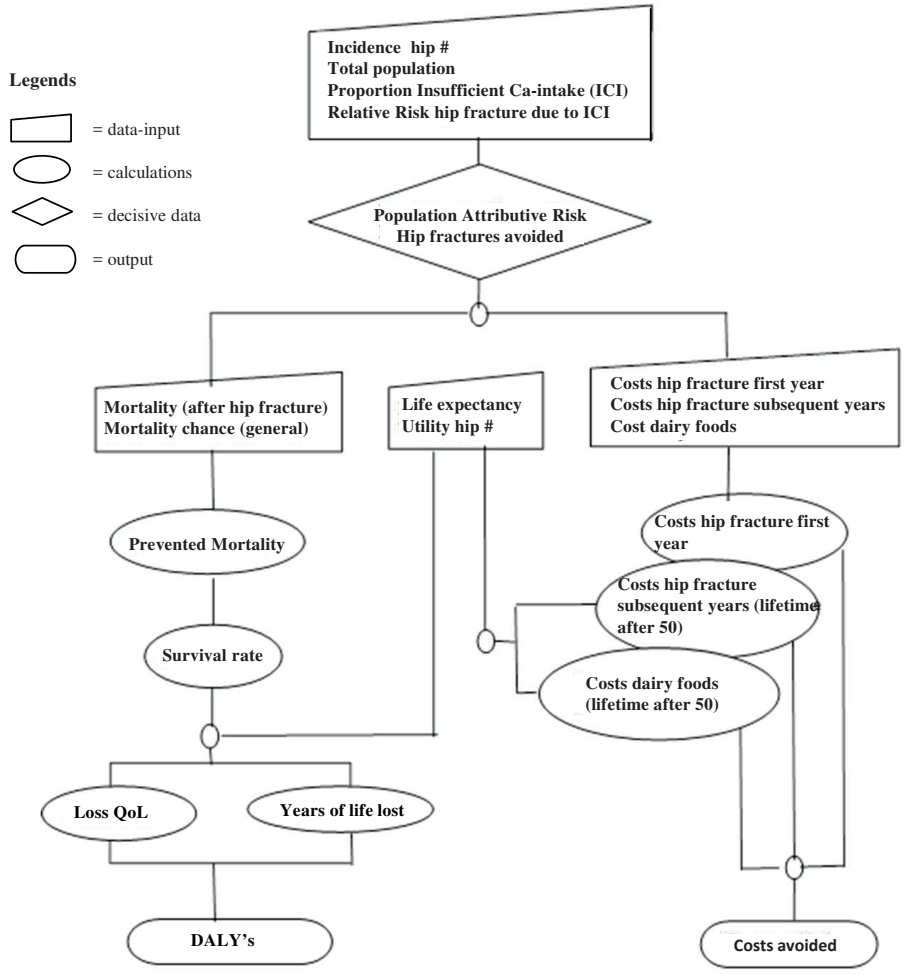
Systematic literature reviews were performed using the following sources: PubMed library, Cochrane library, Embase, and Scopus; Health-economic databases, such as EURONHEED, the NHS Economic Evaluation Database (NHS EED), and the CEA Registry maintained by the Center for the Evaluation of Value and Risk in Health. We used the following search criteria: major search terms were osteoporosis, fracture, bone, dairy, milk, calcium, vitamin D, intervention, supplementation, mortality, quality of life, QALY, medical consumption, costs, cost-effective, cost-benefit, and economic evaluation; peer-reviewed articles were included; only articles in English or Dutch were taken into account; the site of the fracture (at least studies had to distinguish hip fractures from other fractures like spine and wrist); review studies that did not include new data were excluded; studies published in 1995 and onwards were included; due to insufficient data available in the literature on all age groups, the search was restricted to age 50 years and older. The studies retrieved by the literature search were used to arrive at valid estimations of the following parameters, which were needed as an input to the model:

- Relationship between calcium intake by dairy foods and osteoporotic fractures indicated by relative risk estimates or odds ratios.
- Costs of treating fractures in the first year and in subsequent years.
- Mortality risk associated with osteoporotic fractures.
- Health-related quality of life ('utilities') of healthy people and of people who are experiencing an osteoporotic fracture; studies had to use a generic (not disease specific), preference-based instrument to come to a utility.

The way how the above-mentioned parameters were retrieved or calculated in each study was critically judged. Studies that divided their results in age classes were preferred. Studies that evaluated the effects of a specific treatment modality (in a subgroup of patients), rather than including a 'broad' population sample of patients with fractures,

were excluded. We derived data from national databases for each country, *i.e.* Statistics Netherlands (CBS; www.cbs.nl), National Institute of Statistics and Economic Studies (INSEE; www.insee.fr), and Statistics Sweden (SCB; www.scb.se). For The Netherlands, we also used results of the Dutch National Food Consumption Survey.[29] The data needed to build our nutrition economic model can be found in the flow diagram presented in Figure 1.

Figure 1. Flow diagram of the nutrition economic model for hip fracture as outcome of osteoporosis



Study population and countries

The populations of interest were men and women (of any ethnicity) from the general population of Western Europe aged 50 years and over. This includes individuals treated and not treated for osteoporosis. We specifically looked for data that divided the

(general) population by sex and 5-year age classes. Health-economic studies should take into account differences between countries. In this case, it can be expected that dairy intakes may differ considerably between different regions in Europe.[3] Moreover, other differences between the populations of several countries may affect the occurrence of osteoporosis, such as lifestyle, the availability and quality of healthcare, climate, genetic predisposition, etc. Furthermore, treatment pathways, costs of healthcare, and cost prices of dairy food products will differ. To get insight in country differences we will present the model outcomes for The Netherlands, Sweden, and France, a choice based on different dairy intakes and on the availability of country specific public health data and nutritional surveys.

Study focus and perspective

Because dairy food products are the major source of calcium in the Western European diet, this study aimed at quantifying the potential impact of increasing dairy foods consumption on the occurrence of osteoporotic hip fractures in people with an inadequate calcium intake. We defined low calcium intake as a daily intake equal to or less than 600 mg, which is approximately half of the daily intake (DRI) recommended by the International Osteoporosis Foundation.[30,31] We used the calcium content of dairy foods as a marker to model the effect on osteoporotic hip fractures.

The study primarily analysed the costs and health impact from a healthcare perspective. In addition to this, we broadened the perspective to a more societal approach by including the costs of dairy foods made by those persons who could be prevented from having a hip fracture associated with low calcium intake. The study took a life-long time horizon, which implies that both costs and effects were taken into account from the occurrence of hip fracture till death. We used the discount rates recommended in the Dutch guidelines for pharmacoeconomic research (that is, 4 % for costs and 1.5 % for effects).[32]

Analytical techniques and main outcome measures

Using the risk estimate found in the literature, we calculated the Population Attributive Fraction (PAF). This represents the percentage of all hip fractures (among exposed and unexposed) that can be attributed to low calcium intake, as expressed in the formula:

$$PAF = [P_e(RR - 1)]/[P_e(RR - 1) + 1]$$

where: P_e = prevalence of risk factor in the population; RR = relative risk for hip fracture due to low calcium intake.[33] Next, we calculated the absolute amount of hip fractures that potentially can be prevented with additional calcium intake. In epidemiology, this

number is known as the 'potential impact fraction' (PIF), *i.e*. the potential reduction in disease prevalence resulting from a risk factor intervention program. It is calculated by multiplying (per age class) the incidence of hip fractures with the corresponding PAF for that age class.[33] In a formula:

PIF = I * N/1,000 * PAF

where: I = incidence of hip fractures (per 1,000); N = total population per age class; PAF = population attributive fraction. This measure will be used in the further calculations in the model, *i.e.* the outcomes disability-adjusted life years (DALYs) and costs avoided will be referring to the total population per age class. In order to assess the potential impact of increased dairy consumption on the prevention of osteoporotic hip fractures, our model includes two main outcome measures. The first is costs avoided. These are calculated by determining the costs of treating hip fractures (*i.e*. healthcare costs made in the first year after a fracture, as well as those made in subsequent years) and subsequently subtracting the costs made for extra dairy food consumption. In the primary analyses, only the costs of dairy food products made by those people in whom a hip fracture actually could be avoided by extra dairy food consumption are taken into account: we calculated how many dairy products people with a low calcium intake would have to consume to reach the DRI. The data on the calcium content of dairy products were taken from the Dutch Food Composition Database (NEVO).[34] We took an average of different types of dairy products—including milk, yogurt, fresh cheese, and cheese—representing the common consumption pattern in the population for each of the three countries. For example, in The Netherlands, extra 650 mg calcium per day equaled: 200 milliliter low-fat milk (=242 mg calcium) + 125 milliliter low-fat yogurt (=166 mg calcium) + 30 gram young cheese (=237 mg calcium). These data were combined with country-specific unit cost prices of dairy products, derived from general market prices (September 2010 prices). To facilitate comparisons, we used the prices of national supermarkets (preferably the market leaders) rather than those of traditional shops. Finally, we arrived at total costs per day/year, representing the total additional costs if people with a low calcium intake raise their intake up to the recommended level by increasing their dairy foods consumption.

The second main outcome of our model is the number of lost DALYs, which represent a widely-used summary indicator of public health.[35] DALYs are the sum of life years lost due to premature mortality and years lived with disability adjusted for severity. In other words, the basic formula for DALYs is:

DALY = YLL + YLD

where: YLL = years of life lost due to premature mortality; YLD = years of healthy life lost as a result of disability. The DALY measure was used to calculate the life years lost and the loss in quality of life due to hip fracture caused by low calcium intake (see Figure 1). We used country- and age-specific mortality rates due to hip fracture. In this respect, it is important to distinguish between excess mortality rates, *i.e.* the proportion of the population suffering from a hip fracture that dies, and general population mortality, *i.e*. the proportion of the general population that dies due to hip fracture.[36] Considering the data available, and for reasons of comparability between countries, we used the mortality rates after hip fracture in the general population.

Sensitivity analyses

We conducted sensitivity analyses to verify to what extent certain assumptions might have influenced the results. Plausible ranges of uncertain parameters were obtained from the published literature or by varying the estimates by a certain percentage in each direction. The following parameters were varied:

(1) The relative risk expressing the relationship between a low calcium intake and the occurrence of hip fractures, and the proportion of the general population with a low calcium intake.
(2) Long-term quality of life impact of hip fractures.
(3) Discount rates.
(4) Dairy food costs.

The results of the sensitivity analyses are expressed in the outcome measures of DALYs lost and total costs avoided.

RESULTS

Table 1 shows the data used as input in the model. For the sake of clarity, the table pools the data from both sexes and all age categories. In the model itself, all input variables were divided into sex and age categories (*i.e*. 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85 years). The risk factor for a hip fracture due to low calcium intake was based on a study by Cumming *et al*., and amounted to 1.08.[37] The incidence of hip fractures in both men and women in Sweden appeared to exceed that of The Netherlands and France. Moreover, in all countries, it shows that the incidence of hip fractures in women is higher compared with men. Furthermore, the incidence of hip fractures and mortality rates after hip fracture increase substantially with age especially in the age categories of 70 and above. As explained above, the mortality figures in Table 1 refer to the mortality after hip fracture in the general population.

Table 1. Summary of data used and its sources (all age categories pooled)

Parameter	Data (mean over both sexes) (>50 years)			Data sources
	NL	**FR**	**SE**	**(NL/FR/SE)**
Proportion of inadequate calcium intake (*i.e.* <600 mg/day) in the general population	8%	40%	31%	(11, 41, 69)
Recommended intake of calcium in the elderly (mg/day)	1,300	1,300	1,300	(30)
Incidence of hip fractures (per 1,000)[f]	53.9	35.2	64.7	RIVM[a] (36, 70)
Size of the general population (absolute numbers)[f]	5,603,463	21,689,920	3,378,795	CBS[b]/INSEE[c]/SCB[d]
Relationship between an inadequate calcium intake and hip fractures: RR (95%CI)	1.08 (1.02-1.16)	1.08 (1.02-1.16)	1.08 (1.02-1.16)	(37)
Costs of hip fractures (in Euro)[f] - first year after the fracture - subsequent years	 €129,210 €22,815	 €114,602 €50,488	 €114,025 €50,700	(59, 71, 72)
General mortality following hip fractures (per 10,000)	28.7	35.9	99.5	CBS (36, 73)
Life-expectancy (years) and mortality (chance) in the general population (at 50 years)	28.9	30.5	30.6	CBS/INSEE/SCB
Health-related quality of life following hip fractures (*i.e.* the reduction in quality of life measured on a scale from 0 to 1) - first year after the fracture - subsequent years	0.038 0.22 0.08	0.033 0.22 0.08	0.033 0.22 0.08	(38)
Unit cost prices of dairy foods; 'intervention costs/day' (in Euro)[e]	€ 0.44	€ 0.64	€ 0.68	Albert Heijn (www.albert.nl) / Carrefour (www.carrefour.fr) / ICA (www.ica.se)

CBS Statistics Netherlands, *INSEE* Statistics France, *IOF* International Osteoporosis Foundation, *SCB* Statistics Sweden

[a] http://www.nationaalkompas.nl

[b] http://www.cbs.nl

[c] http://www.insee.fr

[d] http://www.scb.se

[e] Corresponding to an extra 650 mg calcium per day; September 2010 prices

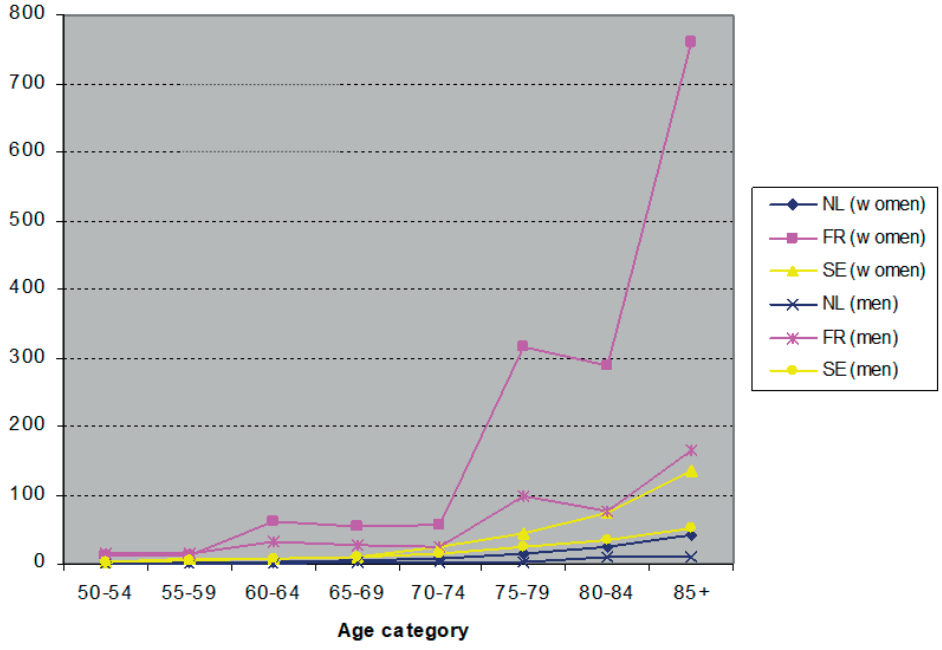
[f] Summed over the eight distinguished age categories

It appeared that, up to the age of 80 years, the mortality data for Sweden exceed those for The Netherlands and France, probably because of the high incidence rates of hip fracture in Sweden compared to the other countries. In the first year after hip fracture, the average loss of quality of life ('utility') was calculated at 0.22; while in the following years, the average loss of quality of life was 0.08. Daily costs of additional dairy products were calculated at €0.44, €0.64, and €0.68, for The Netherlands, France, and Sweden, respectively.

Main outcomes

With a distinction according to age class, figure 2 shows the PIF, indicating the number of hip fractures that could potentially be prevented each year with additional calcium intake. All age classes taken together, the PIF is highest in French women (1,565), followed by Swedish women (307). Across all age classes, the PIF number was relatively low in The Netherlands (103), compared with France and Sweden.

Figure 2. Potential impact fraction (absolute numbers)



The prevented mortality is relatively low for all three countries: all age classes and both sexes taken together, the number of deaths prevented per 10,000 persons experiencing a hip fracture is 5.1 (Sweden), 2.4 (France), and 0.4 (The Netherlands), respectively. This can be explained by the fact that the PAF (*i.e.* the percentage of hip fractures attributed to low calcium intake) is rather low (The Netherlands, 0.8 %; France, 3.1 %; and Sweden, 2.2 %).

Figure 3 shows the yearly number of DALYs lost, representing the burden of hip fractures due to low calcium intake. In all countries, the number of DALYs lost appears to increase with age. In total, the yearly societal burden of hip fractures due to low calcium intake appeared to be 6,263 DALYs for France, 1,246 DALYs for Sweden, and 374 DALYs for The Netherlands.

Figure 3. DALYs lost, representing the burden of hip fractures in relation to low calcium intake

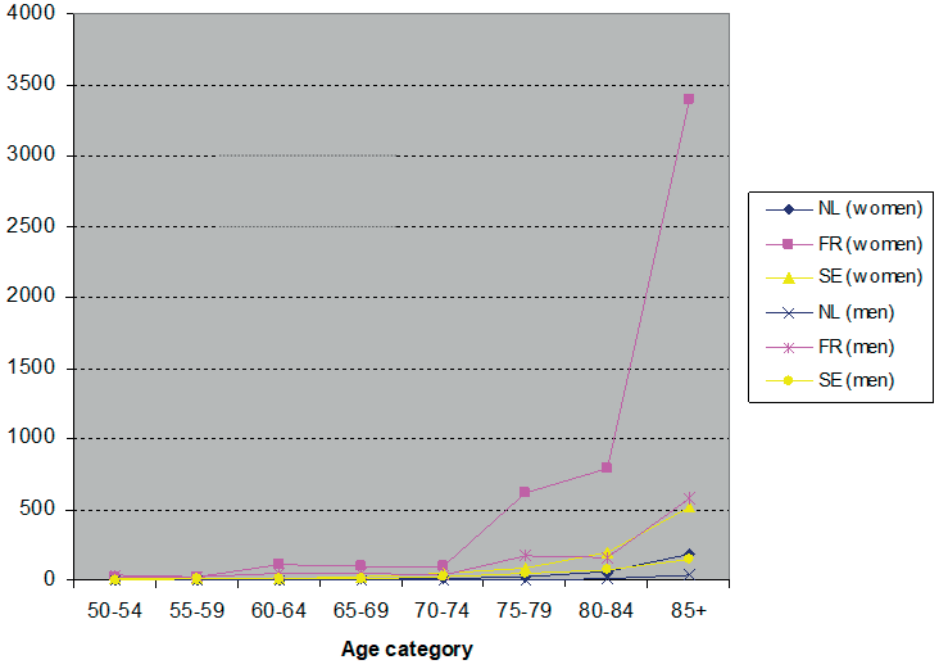


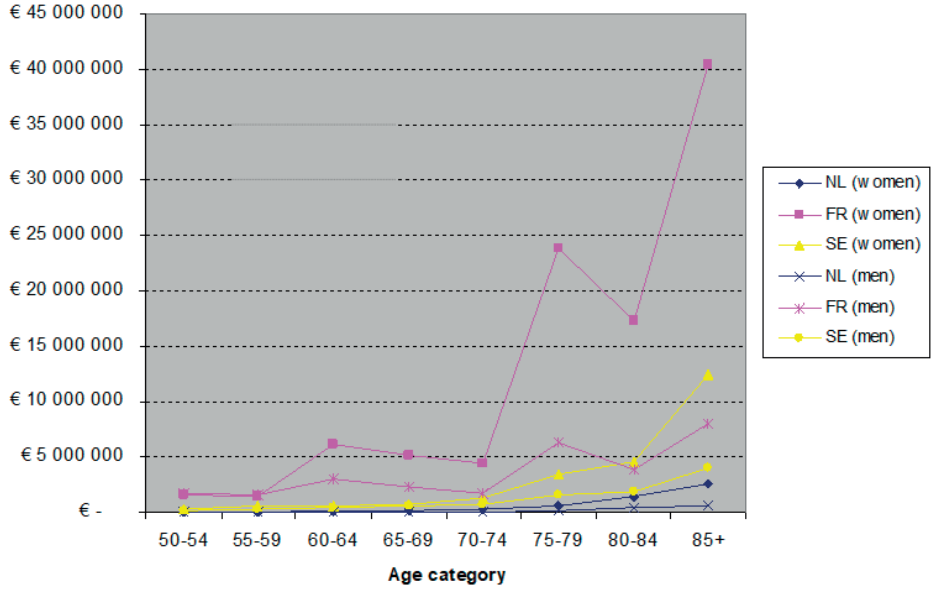
Figure 4 shows the total costs that can potentially be avoided when the risk of hip fractures is decreased by the additional consumption of dairy foods. These discounted costs (which are actually savings) represent the difference between the costs of treating hip fractures and the costs of extra dairy foods. The potential savings on the costs of treating hip fractures exceeded the costs of extra dairy foods in all age classes in all three countries. The total costs potentially avoided were largest in women in France (€100,311,274) followed by women in Sweden (€23,912,460) and The Netherlands (€5,121,041). The main part of these costs can be prevented in the older age categories, *i.e.* from 70 years onwards.

Sensitivity analyses

We varied the PAF by changing the risk factor for a hip fracture associated with low calcium intake (using the 95 % confidence interval of 1.02 to 1.16),[38] as well as by changing the proportion of people with a low calcium intake. Both outcomes of the model (*i.e.* number of DALYs lost and costs avoided) are sensitive for the relative risk of a hip fracture, from age category 70–74 onwards. For example, in the case of The Netherlands, the number of DALYs lost in women aged 85 years and above (in the primary analysis calculated at 185) ranged from 46 to 367. In this subgroup, varying the relative risk made the costs avoided fluctuate between €0.6 million and €5.1 million

(in the primary analysis calculated at €2.6 million). When changing the proportion of people with a low calcium intake with 10%, the number of DALYs and the costs avoided will concomitantly change with approximately 10%. The quality of life after hip fracture during subsequent years was changed using a range of 0.05 and 0.12, where 0.08 was used in the primary analyses.[39] This did not substantially change the outcomes for the three countries under study. In the primary analyses, a discount rate of 4% for costs and 1.5% for health effects was used. We compared this to the results without discounting. The analysis showed that both outcomes (DALYs and costs avoided) were, as expected, slightly lower than when discounting is applied.

Figure 4. Costs avoided (first and subsequent years after hip fracture) through improved dairy foods consumption



Finally, a calculation of costs avoided was made in case dairy food costs were omitted from the model. The reason to do so is that the extra dairy food consumption will most likely be a substitute for other food products. This analysis revealed slightly higher costs savings (3%).

DISCUSSION

In this study, we quantified the potential nutrition economic impact of increasing dairy consumption by people with low calcium intake on the occurrence of osteoporotic hip

fractures. The core of the model was the absolute amount of hip fractures that potentially can be prevented. We particularly paid attention to the potential preventive effect of increasing calcium intake on the occurrence of hip fractures, DALYs, and costs in the population at risk. By including several, geographically distinct European countries with different food patterns, it was shown how the nutrition economic impact of dairy foods on hip fractures varies between countries with different incidence rates of hip fractures, different numbers of people with low calcium intake, and different costs of healthcare and costs of dairy foods. Our study concentrated on middle-aged and older groups, aged 50 years and over. One may question to which extent the principles of health economics apply to food products and dietary habits. Will it simply come down to applying the principles and methods of health economics, or would it be required to develop 'nutrition economics', as a novel subarea of health economics?[25] Next to similarities between health economics in general and 'nutrition economics' in particular, there also will be differences, for example relating to differences in study populations and relating to the fact that food-related changes are often relatively small and only observable over a long time window.[39,40] There is a need to work towards a generic methodology to assess the impact of foods on health, well-being, and costs. In making this effort, osteoporosis offers an excellent case study: it represents a heavy burden and has a high prevalence, the disease is progressing slowly and has an early onset (several decades before it actually manifests itself), and is associated with food consumption.[9] In accordance with earlier studies,[41] the incidence of hip fractures was highest for Sweden, compared to The Netherlands and France. One explanation for these inter-country differences may be related to different levels of calcium intake between countries' populations. However, there will be other explanations as well, which is why there is no one-to-one relationship between calcium intake and rates of hip fractures (as the numbers for the countries included in this study demonstrate). Plausible other hypotheses for these inter-country differences include genetic predisposition and lifestyle factors (nutritional patterns in general, physical activity, etcetera).[42] The highest PIF was found in French women, which can be explained by the relatively large proportion of the French female population with a low calcium intake. In The Netherlands, this PIF number was much lower, relating to the fact that the Dutch consume large amounts of dairy foods.[43,44] It should be noted that the food consumption studies used measured calcium intake from all food products, not solely dairy foods. However, dairy foods contributed by far the most to calcium intake.[11,43] The yearly societal burden of hip fractures associated with low calcium intake appeared to be 374 DALYs for The Netherlands, 6,263 DALYs for France, and 1,246 DALYs for Sweden. The potential savings on the costs of treating hip fractures exceeded the costs of extra dairy foods in all three countries. Total costs avoided were largest in France, mainly due to the relatively high PIF found in France. As mentioned before, the main calculations rested on the assumptions that all these hip fractures are indeed

prevented. This might raise questions about compliance. It is known that compliance with current anti-osteoporotic drugs is rather low, and optimal anti-fracture efficacy is not always achieved in clinical practice.[23,45,46] In a recent study,[47] dairy food has been shown to be an appropriate vehicle to supplement extra calcium and other minerals, with good compliance compared to that reported for supplements.[48] The daily costs of additional dairy were lowest in The Netherlands, compared to France and Sweden. This corresponds with the findings of a European Commission report, which analysed price differences of supermarket goods across Europe.[49] In the primary analysis, costs of additional dairy foods were applied only to those persons who actually could be prevented from having a hip fracture due to low calcium intake. This might overestimate the outcome of the model, as, from a primary prevention point of view, one needs to expose the whole population at risk to extra calcium intake by means of extra dairy consumption. It might be assumed though that when the people at risk start taking extra dairy, this will be a substitution—either full or partly—for other food products. Hence, in this situation, the total cost of dairy foods might only be slightly higher. If a strict health care perspective is adopted, the costs of purchasing dairy foods as part of a normal diet do not need to be taken into account. The scope of the analysis can be limited to the health care costs made for hip fractures.

Some remarks should be made on the data used as input in the calculations, especially regarding the relative risk for hip fracture associated with low calcium intake. First, reviews with pooled study results do not take into account different starting levels of calcium intake. This might hamper the interpretation of the effect size of low calcium intake on the occurrence of hip fractures. The data existing in the literature did not allow us to correct for a different start point in calcium intake of these elderly in our model. This probably resulted in an underestimation of the effect size of the main outcomes in this study. Second, the relative risk for hip fracture was derived from the meta-analysis of Cumming *et al*.[37] Although more recent studies are available on the relationship between calcium intake and osteoporotic fracture, this study mentioned a dose–response relationship. In another meta-analysis, it was found that a supplement of 500 to 1,200 mg calcium would reduce the risk of hip fracture with 12% (RR 0.88; 95% CI 0.83–0.95).[50] This study only took into account randomized controlled trials, with calcium supplementation as intervention. However, both studies are concordant. Recently, a meta-analysis by Bischoff-Ferrari *et al*. did not find a significant reduction in hip fracture by drinking milk for men and women.[51] However, by deleting a Swedish study (considered to be an outlier) from their analyses, the authors found a statistically significant risk reduction of 5 %. Also, in a meta-analysis by Kanis *et al*.,[44] it was found that a low intake of milk was not associated with a marked increase in hip fracture risk. However, low intake was defined as drinking less than one glass of milk daily.

Dairy products such as cheese and yogurt were not taken into account. We defined low calcium intake to be under 600 mg, we took a risk reduction of 8% based on the data of Cumming *et al*.,[37] thereby following a conservative approach. Finally, our approach was supported by the results of a recent population-based cohort study by Warensjö *et al*. In this study, it was found that a dietary calcium intake below approximately 700 mg per day in women was associated with an increased risk of hip fracture.[52] This risk estimate was somewhat higher than in our study. However, this comprehensive study was not specifically directed at dairy calcium intake.

We only used low calcium intake as risk factor for the occurrence of hip fractures. However, there are other factors that intervene with the effect of calcium on bone quality and hip fractures, in particular vitamin D, which plays a crucial role in calcium absorption.[51] It has been shown that there was not much difference between calcium supplementation alone (almost the DRI) or calcium combined with vitamin D on reducing osteoporotic fractures.[50,53] This is in line with the conditions of use as determined by the European Food Safety Authority that indicate 1,200 mg of calcium per day, or 1,200 mg of calcium and 20 µg of vitamin D per day for women aged 50 years and older (http://www.efsa.europa.eu/). However, if dietary calcium is a threshold nutrient, then that threshold for optimal calcium absorption may be achieved at a lower calcium intake when vitamin D levels are adequate.[51] In this respect, it should be mentioned that the occurrence of dairy food fortification with vitamin D might have been of some influence on the results of our model. However, accurate information on the consumption of such products was not readily available. Besides such a fortification, dairy products themselves contain additional nutrients that are beneficial to bone health, e.g. high protein content.[54] Unfortunately, the literature does not provide valid risk-estimates for osteoporotic fractures given the additional elements in dairy foods. In this regard, the results of this study might give an underestimation about the effect size of dairy calcium. Moreover, other factors mediate the effect of calcium on bone health, and concomitantly on osteoporotic fractures. These factors include exposure to sunlight, level of exercise, and genetic predisposition.[55] Considering the foregoing, it may be expected that there are differences in the relative risk of hip fractures between the populations of different countries.

Our analysis concentrated on the effects of dairy calcium on hip fractures. Two observations need to be made about this. First, we did not include osteoporotic fractures other than hip fractures, due to the unavailability of sufficient data. As a result, our model may have underestimated the beneficial effects of dairy calcium. On the other hand, a side effect of consuming more dairy products might be the intake of more saturated fat, considered a risk factor for vascular diseases. Although dairy products make a

contribution to total fat consumption, this contribution is likely to be relatively small. Moreover, a review by Elwood *et al.*[5] showed that there was no convincing evidence of any increased risk of ischaemic heart disease or ischaemic stroke in subjects who have the highest milk consumption.

For all countries in this study, the loss in quality of life following a hip fracture was based on data from a Swedish study[38] because country-specific data were not available. This should not be considered too much of a limitation, as the quality-of-life impact of hip fractures is not expected to differ much between countries—not as much as costs might do. Other 'international' health-economic studies in the field of osteoporosis followed a similar approach: in these studies, the effect of fractures on quality of life was not based on country-specific sources; whereas for the costs, country-specific data were available.[56-59]

CONCLUSIONS

Our study shows that, especially for France and Sweden, the societal burden of hip fractures associated with low calcium intake is quite substantial. Improving the dairy consumption is likely to be effective in decreasing this public health burden and the associated health care expenditures. Our findings support the use of a food-based approach to help maintain bone health or prevent age-related bone loss. This is in line with the position of the French Agency for the Safety of Health Products (AFSSAPS) which recommends to correct calcium and/or vitamin D deficiencies before prescribing anti-osteoporotic drugs.[60] It would be worth performing a cost-effectiveness analysis of a community-based educational health campaign. Behavioral changes, especially related to diet and exercise, form the backbone of public health recommendations for the prevention and treatment of osteoporosis,[61] and are supported by several RCTs[62,63] and meta-analyses.[50,64,65]

Yet, the cost-effectiveness of such recommendations remains largely unexplored. Our model had to rely on the existing figures that do not take into account the long-term advantages of prevention, mainly focusing on the senior population where bone density is already affected and where dietary interventions will complete the clinical management of diagnosed osteoporosis.[66] Yet, it is no less important to focus on younger people as well, because eating practices established in childhood are likely to be maintained throughout life, and an adequate calcium intake during childhood and adolescence, necessary for the development of peak bone mass, may contribute to bone strength and reduce the risk of osteoporosis and fractures later in life.[67,68]

Although the methods may be further refined, this model appears to be a solid and straightforward, easy-to-use method to assess the health, well-being and cost outcomes of food products from a health economics perspective.

REFERENCES

1 Steijns JM. (2008) Dairy products and health: focus on their constituents or on the matrix? *Int Dairy J.* 18, 425–435.

2 Gracia A, Albisu LM. (2001) Food consumption in the European Union: main determinants and country differences. *Agribusiness* 7, 469–488.

3 Hjartåker A, Lagiou A, Slimani N, Lund E, Chirlaque MD, Vasilopoulou E, Zavitsanos X, Berrino F, Sacerdote C, Ocke MC, Peeters PH, Engeset D, Skeie G, Aller A, Amiano P, Berglund G, Nilsson S, McTaggart A, Spencer EA, Overvad K, Tjonneland A, Clavel-Chapelon F, Linseisen J, Schulz M, Hemon B, Riboli E. (2002) Consumption of dairy products in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort: data from 35955 24-hour dietary recalls in 10 European countries. *Public Health Nutr*. 5, 1259–1271.

4 German JB, Gibson RA, Krauss RM, Nestel P, Lamarche B, Staveren WAv, Steijns JM, de Groot LC, Lock AL, Destaillats F. (2009) A reappraisal of the impact of dairy foods and milk fat on cardiovascular disease risk. *Eur J Nutr*. 48, 191–203.

5 Elwood PC, Givens DI, Beswick AD, Fehily AM, Pickering JE, Gallacher J. (2008) The survival advantage of milk and dairy consumption: an overview of evidence from cohort studies of vascular diseases, diabetes and cancer. *J Am Coll Nutr*. 27, 723S– 734S.

6 Tremblay A, Gilbert JA. (2009) Milk products, insulin resistance syndrome and type 2 diabetes. *J Am Coll Nutr*. 28(Suppl 1), 91S– 102S.

7 Boonen S, Vanderschueren D, Haentjens P, Lips P. (2006) Calcium and vitamin D in the prevention and treatment of osteoporosis: a clinical update. *J Intern Med*. 259, 539–552.

8 Heaney RP. (1992) Calcium in the prevention and treatment of osteoporosis. *J Intern Med*. 231, 169–180.

9 Heaney RP. (2000) Calcium, dairy products and osteoporosis. *J Am Coll Nutr*. 19, 83S–99S.

10 Kalkwarf HJ, Khoury JC, Lanphear BP. (2003) Milk intake during childhood and adolescence, adult bone density, and osteoporotic fractures in US women. *Am J Clin Nutr.* 77:257–265.

11 Fardellone P, Cotte FE, Roux C, Lespessailles E, Mercier F, Gaudin AF. (2010) Calcium intake and the risk of osteoporosis and fractures in French women. *Joint Bone Spine* 77, 154–158.

12 Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, Ortiz Z, Peterson J, Adachi J, Tugwell P, Guyatt G. (2002) Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev*. 23, 552–559.

13 McCarron DA, Heaney RP. (2004) Estimated healthcare savings associated with adequate dairy food intake. *Am J Hypertens.* 17, 88–97.

14 World Health Organization (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis, WHO Technical report series no. 843. World Health Organization, Geneva.

15 Reginster JY, Burlet N. (2006) Osteoporosis: a still increasing prevalence. *Bone* 38, S4–S9.

16 Fechtenbaum J, Cropet C, Kolta S, Horlait S, Orcel P, Roux C. (2005) The severity of vertebral fractures and health-related quality of life in osteoporotic postmenopausal women. *Osteoporos Int*. 16, 2175–2179.

17 Papaioannou A, Kennedy CC, Ioannidis G, Sawka A, HopmanWM, Pickard L, Brown JP, Josse RG, Kaiser S, Anastassiades T, Goltzman D, Papadimitropoulos M, Tenenhouse A, Prior JC, Olszynski WP, Adachi JD. (2009) The impact of incident fractures on health-related quality of life: 5 years of data from the Canadian multicentre osteoporosis study. *Osteoporos Int.* 20, 703–714.

18 Borgström F, Sobocki P, Ström O, Jönsson B. (2007) The societal burden of osteoporosis in Sweden. *Bone* 40, 1602–1609.
19 De Laet CE, Van Hout BA, Hofman A, Pols HA. (1996) Costs of osteoporosis-related fractures in The Netherlands, 1993; possibilities of cost control [in Dutch]. *Ned Tijdschr Geneeskd.* 140, 1684–1688.
20 Levy P, Levy E, Audran M, Cohen-Solal M, Fardellone P, Le Parc JM. (2002) The cost of osteoporosis in men: the French situation. *Bone* 30, 631–636.
21 Hosking D, Alonso CG, Brandi ML. (2009) Management of osteoporosis with PTH: treatment and prescription patterns in Europe. *Curr Med Res Opin*. 25, 263–270.
22 Boonen S, Rizzoli R, Meunier PJ, Stone M, Nuki G, Syversen U, Lehtonen-Veromaa M, Lips P, Johnell O, Reginster JY. (2004) The need for clinical guidance in the use of calcium and vitamin D in the management of osteoporosis: a consensus report. *Osteoporos Int*. 15, 511–519.
23 Rossini M, Bianchi G, Di Munno O, Giannini S, Minisola S, Sinigaglia L, Adami S. (2006) Determinants of adherence to osteoporosis treatment in clinical practice. *Osteoporos Int.* 17, 914–921.
24 Geusens P. (2011) Long term treatment for fracture prevention: adherence versus evidence [abstract]. *Ann Rheum Dis*. 70, 41.
25 Lenoir-Wijnkoop I, Dapoigny M, Dubois D, van Ganse E, Gutiérrez-Ibarluzea I, Hutton J, Jones P, Mittendorf T, Poley MJ, Salminen S, Nuijten MJ. (2011) Nutrition economics: characterizing the economic and health impact of nutrition. *Br J Nutr.* 105, 157–166.
26 Gyles CL, Lenoir-Wijnkoop I, Carlberg JG, Senanayake V, Gutierrez-Ibarluzea I, Poley MJ, Dubois D, Jones PJ. (2012) Health economics and nutrition: a review of published evidence. *Nutr Rev*. 70(12), 693-708.
27 Warner KE, Hutton RC. (1980) Cost-benefit and cost-effectiveness analysis in health care. Growth and composition of the literature. *Med Care* 18, 1069–1084.
28 Elixhauser A, Halpern M, Schmier J, Luce BR. (1998) Health care CBA and CEA from 1991 to 1996: an updated bibliography. *Medical Care* 36, MS1, MS9, MS18–MS147.
29 Ocké MC, Hulshof KFAM, Bakker MI, Stafleu A, Streppel MT. (2005) Towards a new system of dietary monitoring in the Netherlands [in Dutch]. National Institute for Public Health and the Environment (RIVM), Bilthoven.
30 International Osteoporosis Foundation. (2011) Calcium. http://www.iofbonehealth.org/patients-public/about-osteoporosis/prevention/nutrition/calcium.html. Accessed 9 August 2011
31 Ross AC, Taylor CL, Yaktine AL, Del Valle HB. (2010) Dietary reference intakes for calcium and vitamin D. Institute of Medicine of the National Academy of Sciences (IOM), Washington.
32 Health Insurance Board. (2006) Guidelines for pharmacoeconomic research. Updated version. Health Insurance Board, Diemen.
33 Rothmann KJ, Greenland S. (2008) Modern epidemiology. Lippincott, Philadelphia.
34 RIVM (2010) Nederlands voedingstoffenbestand (NEVO). http://nevo-online.rivm.nl/
35 Murray CJL, Lopez AD. (1997) Global mortality, disability, and the contribution of risk factors: global burden of disease study. *Lancet* 349, 1436–1442.
36 Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. (2003) The components of excess mortality after hip fracture. *Bone* 32, 468–473.
37 Cumming RG, Nevitt MC. (1997) Calcium for prevention of osteoporotic fractures in postmenopausal women. *J Bone Miner Res*. 12, 1321–1329.
38 Ström O, Borgström F, Zethraeus N, Johnell O, Lidgren L, Ponzer S, Svensson O, Abdon P, Ornstein E, Ceder L, Thorngren KG, Sernbo I, Jönsson B. (2008) Long-term cost and effect on quality of life of osteoporosis-related fractures in Sweden. *Acta Orthop*. 79, 269–280.
39 Heaney RP. (2008) Nutrients, endpoints, and the problem of proof. *J Nutr.* 138, 1591–1595.

40 Genton L, van Gemert W, Pichard C, Soeters P. (2005) Physiological functions should be considered as true end points of nutritional intervention studies. *Proc Nutr Soc.* 64, 285–296.
41 Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Ogelsby AK. (2002) International variations in hip fracture probabilities: implications for risk assessment. *J Bone Miner Res.* 17, 1237–1244.
42 Johnell O, Gullberg B, Kanis JA, Allander E, Elffors L, Dequeker J, Dilsen G, Gennari C, Lopes Vaz A, Lyritis G. (1995) Risk factors for hip fracture in European women: the MEDOS Study. Mediterranean Osteoporosis Study. *J Bone Miner Res*. 10, 1802–1815.
43 Fransen HP, Waijers PMCM, Jansen EHJM, Ocké MC. (2007) Assessment of nutritional status in the new system of dietary monitoring in the Netherlands. RIVM, Zeist/Bilthoven.
44 Kanis JA, Johansson H, Oden A, De Laet C, Johnell O, Eisman JA, Mc Closkey E, Mellstrom D, Pols H, Reeve J, Silman A, Tenenhouse A. (2005) A meta-analysis of milk intake and fracture risk: low utility for case finding. *Osteoporos Int*. 16, 799–804.
45 Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks C. (2004) The impact of compliance with osteoporosis therapy on fracture rates in actual practice. *Osteoporos Int* 15, 1003–1008.
46 Leslie WD, O'Donnell S, Jean S, Lagace C, Walsh P, Bancej C, Morin S, Hanley DA, Papaioannou A, Osteoporosis Surveillance Expert Working Group. (2009) Trends in hip fracture rates in Canada. *JAMA* 302, 883–889.
47 Kruger MC, Schollum LM, Kuhn-Sherlock B, Hestiantoro A, Wijanto P, Li-Yu J, Agdeppa I, Todd JM, Eastell R. (2010) The effect of a fortified milk drink on vitamin D status and bone turnover in post-menopausal women from South East Asia. *Bone* 46, 759–767.
48 Prince RL, Devine A, Dhaliwal SS, Dick IM. (2006) Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med*. 166, 869–875.
49 Commission E (2002) Price differences for supermarket goods in Europe. Internal working document of the Internal Market Directorate General. European Commission, Brussels.
50 Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. (2007) Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet* 370, 657–666.
51 Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Kanis JA, Orav EJ, Staehelin HB, Kiel DP, Burckhardt P, Henschkowski J, Spiegelman D, Li R, Wong JB, Feskanich D, Willett WC. (2011) Milk intake and risk of hip fracture in men and women: a meta-analysis of prospective cohort studies. *J Bone Miner Res.* 26, 833–839.
52 Warensjö E, Byberg L, Melhus H, Gedeborg R, Mallmin H, Wolk A, Michaelsson K. (2011) Dietary calcium intake and risk of fracture and osteoporosis: prospective longitudinal cohort study. *BMJ* 342, d1473.
53 Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. (2009) Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* 2, CD000227.
54 Dawson-Hughes B, Harris SS. (2002) Calcium intake influences the association of protein intake with rates of bone loss in elderly men and women. *Am J Clin Nutr*. 75, 773–779.
55 Walker-Bone K, Walter G, Cooper C. (2002) Recent developments in the epidemiology of osteoporosis. *Curr Opin Rheumatol*. 14, 411–415.
56 Borgström F, Zethraeus N, Johnell O, Lidgren L, Ponzer S, Svensson O, Abdon P, Ornstein E, Lunsjo K, Thorngren KG, Sernbo I, Rehnberg C, Jonsson B. (2006) Costs and quality of life associated with osteoporosis-related fractures in Sweden. *Osteoporos Int*. 17, 637–650.

57 Borgström F, Johnell O, Kanis JA, Jönsson B, Rehnberg C. (2006) At what hip fracture risk is it cost-effective to treat? International intervention thresholds for the treatment of osteoporosis. *Osteoporos Int*. 17, 1459–1471.

58 Lekander I, Borgström F, Ström O, Zethraeus N, Kanis JA. (2008) Cost effectiveness of hormone therapy in women at high risks of fracture in Sweden, the US and the UK: results based on the Women's Health Initiative randomised controlled trial. *Bone* 42, 294–306.

59 Ström O, Borgström F, Sen SS, Boonen S, Haentjens P, Johnell O, Kanis JA. (2007) Cost-effectiveness of alendronate in the treatment of postmenopausal women in 9 European countries: an economic evaluation based on the fracture intervention trial. *Osteoporos Int*. 18, 1047–1061.

60 Agence Française de Sécurité Sanitaire des Produits de Santé. (2006) Traitement médicamenteux de l'ostéoporose post-ménopausique. Recommendations. Actualisation 2006. Agence Française de Sécurité Sanitaire des Produits de Santé. Saint-Denis Cedex, France

61 Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, Rizzoli R. (2008) European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*. 19, 399–428.

62 Bischoff-Ferrari HA, Rees JR, Grau MV, Barry E, Gui J, Baron JA. (2008) Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. *Am J Clin Nutr.* 87, 1945–1951.

63 Zhu K, Bruce D, Austin N, Devine A, Ebeling PR, Prince RL. (2008) Randomized controlled trial of the effects of calcium with or without vitamin D on bone structure and bone-related chemistry in elderly women with vitamin D insufficiency. *J Bone Miner Res*. 23, 1343–1348.

64 Nordin BE. (2009) The effect of calcium supplementation on bone loss in 32 controlled trials in postmenopausal women. *Osteoporos Int*. 20, 2135–2143.

65 Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, Hamel C, Ortiz Z, Peterson J, Adachi J, Tugwell P, Guyatt G. (2004) Calcium supplementation on bone loss in postmenopausal women. *Cochrane Database Syst Rev*. 1, CD004526.

66 Straub DA. (2007) Calcium supplementation in clinical practice: a review of forms, doses, and indications. *Nutr Clin Pract*. 22, 286–296.

67 Bonjour JP, Carrie AL, Ferrari S, Clavien H, Slosman D, Theintz G, Rizzoli R. (1997) Calcium-enriched foods and bone mass growth in prepubertal girls: a randomized, double-blind, placebo-controlled trial. *J Clin Invest*. 99, 1287–1294.

68 Rizzoli R, Bianchi ML, Garabedian M, McKay HA, Moreno LA. (2010) Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. *Bone* 46, 294–305.

69 Angbratt M, Timpka T, Blomberg C, Kronhed AC, Waller J, Wingren G, Moller M. (2007) Prevalence and correlates of insufficient calcium intake in a Swedish population. *Public Health Nurs*. 24, 511–517.

70 Maravic M, Taupin P, Landais P, Roux C. (2011) Change in hip fracture incidence over the last 6 years in France. *Osteoporos Int*. 22, 797–801.

71 Jansen JP, Gaugris S, Bergman G, Sen SS. (2008) Cost effectiveness of a fixed dose combination of alendronate and cholecalciferol in the treatment and prevention of osteoporosis in the United Kingdom and The Netherlands. *Curr Med Res Opin*. 24, 671–684.

72 Borgström F, Jönsson B, Ström O, Kanis JA. (2006) An economic evaluation of strontium ranelate in the treatment of osteoporosis in a Swedish setting: based on the results of the SOTI and TROPOS trials. *Osteoporos Int*. 17, 1781–1793.

73 Ziadé N, Jougla E, Coste J. (2010) Population-level impact of osteoporotic fractures on mortality and trends over time: a nationwide analysis of vital statistics for France, 1968–2004. *Am J Epidemiol.* 172, 942–951.

Chapter 7

Health economic modelling to assess short-term costs of maternal overweight, gestational diabetes and related macrosomia – a pilot evaluation

Irene Lenoir-Wijnkoop, Eline M van der Beek, Johan Garssen, Mark J Nuijten, Ricardo D Uauy

Published in: Front Pharmacol. 2015;6, 103

ABSTRACT

Background Despite the interest in the impact of overweight and obesity on public health, little is known about the social and economic impact of being born large for gestational age or macrosomic. Both conditions are related to maternal obesity and/or gestational diabetes (GDM) and associated with increased morbidity for mother and child in the perinatal period. Poorly controlled diabetes during pregnancy, prepregnancy maternal obesity and/or excessive maternal weight gain during pregnancy are associated with intermittent periods of fetal exposure to hyperglycemia and subsequent hyperinsulinemia, leading to increased birth weight (e.g. macrosomia), body adiposity and glycogen storage in the liver. Macrosomia is associated with an increased risk of developing obesity and type 2 diabetes mellitus later in life.

Objective Provide insight in the short-term health-economic impact of maternal overweight, gestational diabetes (GDM) and related macrosomia. To this end, a health economic framework was designed. This pilot study also aims to encourage further health technology assessments, based on country- and population-specific data.

Results The estimation of the direct health-economic burden of maternal overweight, GDM and related macrosomia indicates that associated healthcare expenditures are substantial. The calculation of a budget impact of GDM, based on a conservative approach of our model, using USA costing data, indicates an annual cost of more than $1,8 billion without taking into account long-term consequences.

Conclusion Although overweight and obesity are a recognized concern worldwide, less attention has been given to the health economic consequences of these conditions in women of child-bearing age and their offspring. The presented outcomes underline the need for preventive management strategies and public health interventions on lifestyle, diet and physical activity. Also, the predisposition in people of Asian ethnicity to develop diabetes emphasizes the urgent need to collect more country-specific data on the incidence of macrosomic births and health outcomes. In addition, it would be of interest to further explore the long-term health economic consequences of macrosomia and related risk factors.

INTRODUCTION

The foundations of health throughout life are laid during the peri-conceptional period, from conception until birth, and after birth in early childhood. Much attention has been paid to the long-term consequences of undernutrition and micronutrient deficiencies during the first 1000 days, covering the timespan from conception until the 2nd birthday.[1,2] The link between compromised nutritional status of the baby's mother and low birth weight on one hand, and impaired health of the child in later life on the other hand has now been clearly established. The far-reaching relationships with multiple health-related outcomes affecting human capital and productivity have been clearly corroborated.[3]

In contrast, despite the general high interest in the public health burden of overweight and obesity, far less is known about the potential clinical and economic consequences of maternal conditions leading to high birth weight (large for gestational age; LGA) or macrosomia.

Macrosomia

Macrosomia is defined as an absolute birth weight >4000g regardless of gestational age.[4,5] The incidence of macrosomia ranges from 12.8 to 37.4% worldwide.[6-8] In developed countries, the prevalence of macrosomia ranges from 5 to 20%; and an increase of 15–25% has been reported over the last three decades, mainly driven by an increase in maternal obesity and type 2 diabetes (T2DM). In addition, the threshold for macrosomia might need to be reconsidered for Asian countries, where average birth weight is in general lower compared to European countries and consequently the cut off weight for LGA (>95th percentile) would be lower.

Maternal overweight, excessive gestational weight gain (GWG) by itself, gestational diabetes (GDM), defined as mild to moderate hyperglycemia leading to diabetes first diagnosed during pregnancy which disappears after giving birth, and elevated fasting plasma glucose levels during pregnancy have all been reported to be significant risk factors for macrosomia.[9] In developing countries maternal short statue, high body mass index (BMI) and T2DM are strong risk factors for macrosomia.[10]

Macrosomia is the main cause of (acute) perinatal complications for both mother and infant. Adverse maternal outcomes associated with macrosomia include preterm birth, higher rates of postpartum hemorrhage, as well as increased risk of caesarean delivery.[11-13] For the macrosomic infant, birth trauma is commonly related to instrumental delivery, e.g. newborns with a birth weight >4000g have 9.0 times higher odds of shoulder

dystocia, while those with a birth weight >4500g have odds that are 39.5 times higher than normal-weight infants.[14] Furthermore, macrosomic infants are more likely to have low 5-minute Apgar scores, an index of hypoxia.[3] Infants with very severe macrosomia (birth weight >5000g) are at increased risk of neonatal, post-neonatal and infant death.[4] Macrosomia also significantly increases the risk for developing obesity in childhood, and non-communicable diseases (NCD) later in life.[1]

Background

A key component of normal metabolic adaptation to pregnancy is the development of mild insulin resistance and changes in the regulation of appetite in the mother, gradually evolving during gestation.[15-17] These normal physiological adaptations serve to shuttle sufficient nutrients to the growing fetus, especially during the last trimester of pregnancy. Poorly controlled diabetes, maternal obesity, and excessive maternal weight gain during pregnancy are associated with intermittent, non-physiological periods of fetal hyperglycemia, and subsequent hyperinsulinemia from the start of pregnancy and onward. The resulting maternal insulin resistance and hormonal responses related to high blood glucose, such as insulin-like growth factors and growth hormone, lead to greater deposition of body fat and glycogen in muscle and liver in the fetus. The greater and more rapid fetal growth (in particular of adipose tissue) subsequently results in increased birth weight.

Overweight, obesity and gestational weight gain

Women with either prepregnancy obesity and/or excessive GWG, have a higher risk for developing GDM, pregnancy-induced hypertension, caesarean delivery, and LGA and macrosomic infants compared to women with normal prepregnancy BMI and adequate pregnancy weight gain.[18]

Using a hospital-based delivery database of 18 362 subjects in the USA, overweight, obese and severely obese women showed higher risks for LGA, GDM and pre-eclampsia in comparison to their normal-weight counterparts.[19] In another study, the proportion of LGA infants born to overweight and obese mothers without GDM was significantly higher than in their normal-weight counterparts in a retrospective study of 9 835 women in Southern California, USA; 21.6% of LGA infants were explained by maternal overweight and obesity.[20] Similarly, a 13-years study of 292 568 singleton pregnancies in China[21] demonstrated that adverse pregnancy outcomes, such as hypertensive disorders, caesarean delivery, macrosomia and LGA infants, were associated with overweight mothers, who during pregnancy gained weight beyond current IOM recommendations.[22]

In a study of 366 886 singleton pregnancies from the Danish Medical Birth Registry from 2004 to 2010, the ratio between abdominal circumference and birth weight decreased with increasing maternal BMI, suggesting that maternal obesity results in a general weight gain of the fetus rather than just fat accumulation around the abdomen.[23] Finally, an observational study at five antenatal centers in Ireland reported that excessive GWG resulted in higher odds for LGA and macrosomia, as well as increased odds for gestational hypertension in women with GDM. The need for treatment with insulin further increased the odds for LGA and macrosomia.[24]

Altogether, these studies emphasize that high prepregnancy BMI and/or high GWG form a substantial risk for macrosomic birth worldwide. The fact that some studies do not report increased rates of macrosomia despite the increasing prevalence of obese pregnancies, may be explained by, for instance, changes in obstetric practice such as caesarian section before week 40 of pregnancy.[25]

Gestational diabetes mellitus

In women already prone to insulin resistance because of obesity or (epi) genetic predisposition,[26] this physiological tendency is augmented and can result in the development of GDM, commonly diagnosed around week 20-24 of pregnancy. A study including 35 253 pregnancies in Australia showed an average incidence of GDM of 5.5% (n=1928).[27] GDM has been reported to affect 4–7% of pregnancies in Caucasian women, while the incidence is consistently higher (8–15%) and rising rapidly in Asian women.[28-30] According to a recent survey, there is a large variation in estimated GDM prevalence, showing a range from <1% to 28% with data derived from single or multi-site, national data and/or estimates from expert assessments in 47 countries.[31] Direct comparison between countries is difficult due to different diagnostic strategies and population groups. Many countries do not perform systematic screening for GDM, and practices often diverge from guidelines. Interestingly, the Hyperglycemia And Pregnancy Outcome (HAPO) study results clearly indicate that relatively mild hyperglycemia was already associated with a significant increase in macrosomia.[32] Adoption of the HAPO criteria for GDM diagnosis will likely lead to higher GDM prevalence compared to current estimates,[31] although still considerable differences in incidence as well as relevance of the different hyperglycemia measures were reported between the participating HAPO centers.[33]

OBJECTIVE

The primary objective of this study is to design a health economic framework that will allow a pilot estimation of the short-term healthcare burden associated with maternal overweight and/or GDM, in particular as related to fetal macrosomia. The secondary goal is to lay a basis for fostering interest in the development of targeted preventive approaches in an effort to reduce the related total costs. The subject is closely related to the problem of rising NCD prevalence and the related disease outcomes, and will be of interest for both developing and industrialized countries.[11,34,]

MATERIALS AND METHODS

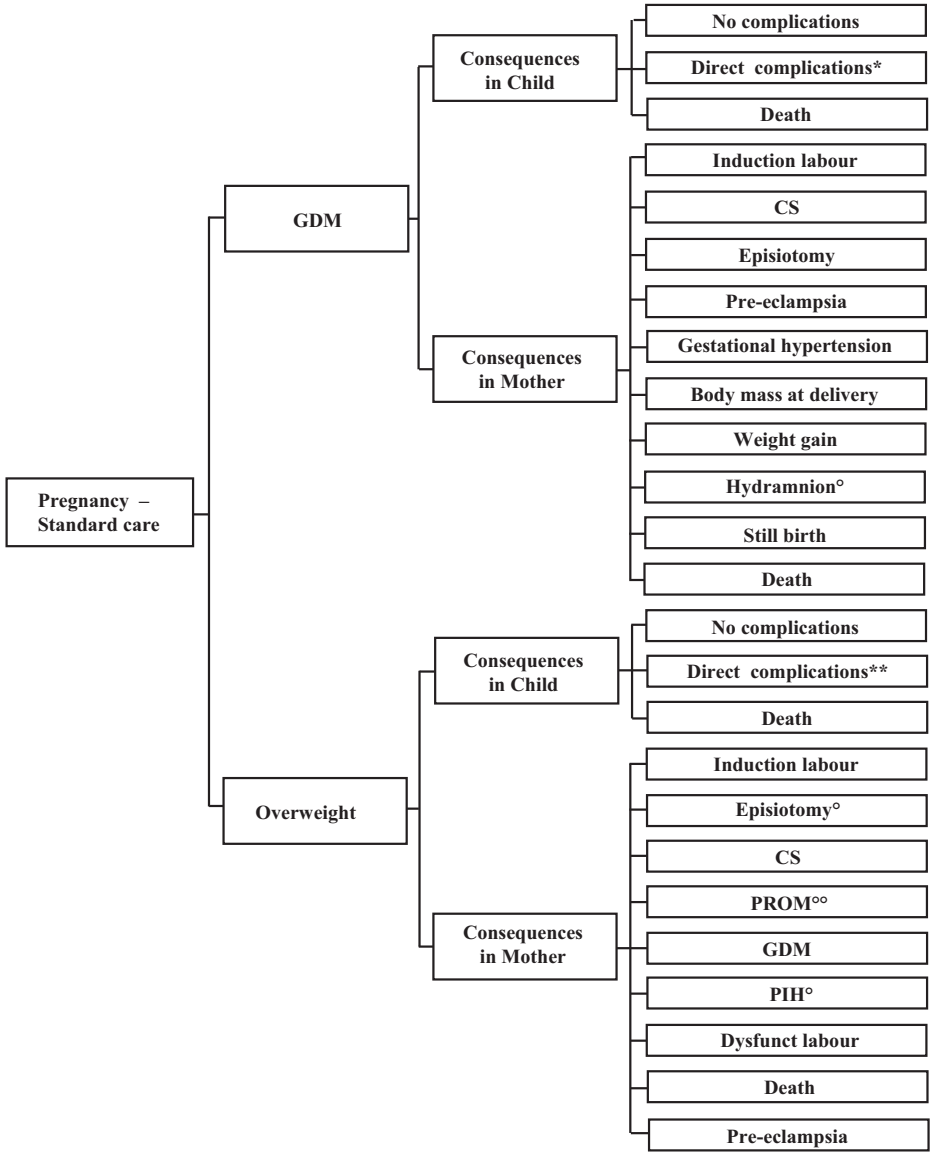
A model to map the health economic consequences of GDM, overweight pregnancies and macrosomia was developed based on decision analytical techniques, a well-accepted methodology in the field of health-economics.[35] To estimate the health economic impact of management of macrosomia, the short-term consequences of GDM, obesity and macrosomia were taken into account. Data sources included published literature, clinical trials, official price/tariff lists, if available, and national population statistics. This study is based on methodological guidance derived from cost-effectiveness studies in nutrition economics.[36]

Model Design

The health economic impact is calculated, using a decision tree model constructed in TreeAge Pro 2005/2006, reflecting treatment patterns and outcomes in the management of obesity during pregnancy, GDM and related delivery of the macrosomic infant. The present decision tree model is shown in Figure 1.

During the pregnancy the occurrence of GDM and/or obesity may lead to various complications in mother and child. The model consists of two sub-models: 1) development of maternal GDM, 2) maternal obesity, accompanied or not with the development of GDM. Delivery after GDM or obesity is the next "health state". The delivery may be normal, leading to "normal child" or "macrosomic" child. Using conventional principles of clinical decision analysis, expected clinical, and economic outcomes are determined as a probability-weighted sum of costs and outcomes further to the initial treatment decisions. As both mother and child may be subject to various clinical events and disease progression after delivery, the number of possible health states is finite. Therefore, the follow-up beyond delivery was based on a Markov process. An advantage of applying a Markov process is that it allows long-term modelling of GDM and obesity

Figure 1. Structure of the model



Reported events are based on literature:

*Includes respectively hypoglycemia, hyperbilirubinemia, prematurity, macrosomia, brachial plexus injury, shoulder dystocia, respiratory distress, NICU admission;

**Includes respectively prematurity, macrosomia, NICU, stillbirth, IUGR;

°Only reported for GDM (Michlin[38]);

°°Not reported for GDM.

for the mother and its complications for both mother and child (complicated delivery, macrosomia, and related morbidity).

Study population

The model included a study population of women of childbearing age who are overweight or obese prior to pregnancy. Women with (pre-existing) diabetes mellitus, both type I and type II, or related morbidity before pregnancy were excluded. The model considers thus a cohort of otherwise healthy women with a probability of getting pregnant.

Cost Assessment

An analysis can be conducted from the perspective of the society in a pre-selected study country, while it is also possible to consider the payer's perspective only. The choice of the perspective will depend on the country-specific health economic guidelines. The current cost assessment, performed as a pilot, is based only on short-term costs caused by the management of the complications as reported in literature, from the national health care perspective.

DATA SOURCES

Various data sources were considered for developing the framework in order to maximize its external validity for any local setting. A narrative review of the scientific literature from several electronic databases was conducted to find studies published between 1994 to July 2014 with the following key words: birth weight, (rapid) weight gain, growth trajectories, body composition, overweight, obesity, metabolic health, cohort, observational studies, Asia, Australia and Europe. Only studies published in English were included. Probabilities of clinical events and utilities are usually accepted as not country-specific and are considered to be transferable beyond their original production location. They can therefore be derived from international studies, while economic measures and information on therapeutic choices depend on a particular region, country or healthcare system.[37]

Incidence

The incidence rate used for our model was 5.5%, derived from the study outcomes reported by Beischer.[27] This is a conservative value, taken into account the incidence rates reported above[28-30] and considering the rising risk of macrosomic pregnancies related to an overall 15-25% increase in the proportion of women giving birth to large infants worldwide.[11]

Complications

Studies reporting the risk of perinatal adverse outcomes for mother and child in the case of obesity,[38-41] mild GDM[42,43] and total GDM[44-46] show that not all complications are statistically significant. Data input on obesity is derived from Salihu *et al*.[39] because of the large sample size of obese women (Table 1), whereas for GDM the data for mild GDM are used,[40,41] taking a conservative approach. Mission *et al*.[44] provided a much higher probability for shoulder dystocia, which was taken into account for further cost estimations, as well as additional information provided by Keshavarz *et al*.[46] on the probability of hydramnion and stillbirth (respectively 0.60 and 0.40%).

Macrosomia management in GDM

Table 2 shows an overview of data from studies on interventions related to macrosomia incidence in GDM.[47,48] Herbst provided data on direct complications related to macrosomia.[49] These data may be considered in addition to previously mentioned data. Using decision analysis techniques, the authors compared three strategies for an infant with an estimated fetal weight of 4500 g: labor induction, elective caesarean delivery, and expectant treatment (Table 3). Mortality outcomes were based on the study by Mitanchez who evaluated the risks of perinatal complications in infants born to mothers with treated or untreated GDM, including also risk of death.[50]

Most of the costing data were derived from the studies by Herbst[49] and Ohno *et al*.[43] In case of lack of information on direct data, the costs were based on treatment practice derived from guidelines or assumptions based on similarities in treatment (Table 4). Maternal short-term costs are related to caesarian section, pre-eclampsia, or gestational hypertension, induction of labor, maternal death. In this model we assume that in case of normal pregnancy and vaginal delivery, there is a routine cost of $7 790.[43] This assumption is, however, based on the 2011 situation in the USA only, and outcomes may be considerably different in case specific costing data of other countries or at other time points would be used. Because of the lack of costing data from other countries, we performed an extreme sensitivity analysis on the costs by varying ± 20%.

RESULTS

The base case analysis gives the results for the period including pregnancy and delivery only, without including costs of diagnosis and management of GDM, nor of complications beyond the obstetric period or consequences for mother and child on the longer term.

Table 1. Complications in mild gestational diabetes mellitus (GDM) and obese mothers

Mild GDM								**Source**
Outcomes								Landon(42)
Neonatal outcomes	**Hypo-glycemia**	**Hyper bilirubinemia**	**Birth weight >4000**	**Preterm delivery**	**NICU admission**	**Resp. distress**	**Fat mass in g**	
Intervention (n = 485)	16.30%	9.60%	5.90%	9.40%	9.00%	1.90%	42,700	
Control (n = 473)	15.40%	12.90%	14.30%	11.60%	11.60%	2.90%	46,400	
Statistical significance	NS	NS	S	NS	NS	NS	S	
Maternal outcomes	**Induction labor**	**Cesarean delivery**	**Shoulder dystocia**	**Preeclampsia**	**Preeclampsia OR Gestational hypertension**	**Body mass at delivery**	**Weight gain (g)**	
Intervention (*n* = 485)	27.30%	26.90%	1.50%	2.50%	8.60%	3130	280	
Control (n = 473)	26.80%	33.80%	4.00%	5.50%	13.60%	3230	500	
Statistical significance	NS	S	S	S	S	S		
Maternal outcomes*	**Preeclampsia**	**Cesarean delivery**						Ohno (43)
Treatment	8.60%	26.90%						
No treatment	13.60%	33.80%						
Neonatal outcomes*	**Macrosomia**	**Brachial plexus injury**	**NICU admission**					
Treatment	5.90%	6.70%	9.00%					
No treatment	14.30%	6.70%	11.6%					
Obese mothers	**Anemia**	**Insulin-diabetes**	**Other diabetes**	**Chronic hypertension**	**Preeclampsia**	**Eclampsia**		Salihu (39)
Non-obese (*n* = 90,022)	1.18%	0.83%	2.18%	0.28%	2.42%	0.06%		
Obese (*n* = 26,954)	1.31%	3.08%	7.18%	2.23%	5.89%	0.08%		
Statistical sign.	NS	S	S	S	S	NS		

*Statistical significance not reported.

Table 2. Treatment GDM – macrosomia

Risk	Comparison	Odds ratio	Confidence interval	Source
Macrosomia	Treatment GDM *vs*. usual care	0.38	0.30–0.49	Horvath (47)
Macrosomia	No treatment GDM *vs*.control	2.66	1.93–3.67	Langer (48)
Macrosomia	Treatment *vs*. control	1.13	0.82–1.55	Langer (48)
LGA (large for gestational age)	No treatment GDM *vs*. control Treatment GDM *vs*. control	3.28 1.06	2.53–3.67 0.81–1.38	Langer (48) Langer (48)

Table 3. Complications macrosomia

Fetal macrosomia	Cesarean delivery	
	Elective induction	35%
	Expectant mgt	33%
	Shoulder dystocia	
	Elective cesarean delivery	0.1%
	Elective induction	
	Ceasarean delivery	0.3%
	Vaginal delivery	14.5%
	Expectant management	
	Ceasarean delivery	0.3%
	Vaginal delivery	3%
	Plexus injury	18%
	Permanent injury	6.7%

Table 4. Costing data

Cost item	Cost ($)	Cost item	Cost ($)
Child_brachplexus	1,757	Mother_anemia	0
Child_hyperbili	2,006	Mother_bodymass	0
Child_hypoglycemia	2,419	Mother_cesarean	4,189
Comp_child_IUFD	82,361	Mother_episiotomy	5,165
Mp_child_IUGR	15,065	Mother_gdm	1,786
Child_macrosomia	4,014	Mother_gest	1,786
Child_NICU	15,065	Mother_gesthyper	1,786
Child_overweight	4,014	Mother_hydramnion	0
Child_premature	3,376	Mother_hypertension	1,786
Child_preterm delivery	3,376	Mother_induction	5,165
Child_resp_distress	3,376	Mother_PIH	19,184
Child_shoulder	1,757	Mother_pre eclampsia	19,184
		Mother_PROM	5,165
		Mother_shoulder	950
		Mother_still birth	0
		Mother_weight gain	0
Assumption routine cost normal pregnancy and vaginal delivery			7,790

The average of total additional costs for overweight is $18 290 per pregnancy/delivery, which consists of average costs for the mother ($13 047) and average costs for the child ($5 243).

The average of total additional costs for GDM is $15 593 per pregnancy/delivery, which consists of the average costs for delivery and complications for the mother ($11 794) and the average direct costs for neonatal complications in the macrosomic child ($3 799; Table 5).

Table 5. Base case analysis

	Mother	Child	Total
Period	Pregnancy and delivery		
Normal	$7,790	$0	$7,790
GDM	$11,794	$3,799	$15,593
Overweight	$13,047	$5,243	$18,290

Example of a budget impact calculation

The translation of costs per case (pregnancy and delivery only) to national level, based on pregnancy rate and the incidence of GDM, leads to the budget impact. To illustrate this, the budget impact of GDM for the USA was calculated, since most of the costing data available are provided by USA studies. The national annual number of pregnancies is 13.68 per 1000 for a population of 313 847 500.[51] In case of a GDM incidence rate of 5.5%,[32] this represents an annual number of GDM cases of 236 139 in the USA. With a cost difference between normal pregnancy/delivery and complicated delivery due to GDM of $7 803 ($15 593 - $7 790), this leads to an annual budget impact of more than $1.8 billion, according to the short-term conservative approach taken in our model. Although these outcomes cannot be extrapolated to other countries because of differences in costs as well as in the organization of national health structures, the principle of calculation remains similar for any part of the world as soon as reliable information becomes available.

Table 6 shows an overview of the sensitivity analyses. Because of lack of statistical distributions, the sensitivity analyses were conducted by varying the parameters ± 20%. The outcomes show that in all sensitivity analyses the economic impact remains substantial.

Table 6. Sensitivity analyses

	Per case	BIA
Base case	$7,803	$1,842,525,634
Incidence		
−20%	$7,803	$1,474,020,507
+20%	$7,803	$2,211,030,761
Cost complications		
−20%	$4,684	$1,106,116,165
+20%	$10,921	$2,578,935,103
Cost normal pregnancy		
−20%	$6,242	$1,474,020,507
+20%	$9,363	$2,211,030,761
Cost complications baby		
−20%	$5,444	$1,285,536,028
+20%	$10,161	$2,399,515,240
Cost complications mother		
−20%	$7,043	$1,663,105,770
+20%	$8,563	$2,021,945,498

DISCUSSION

The current model proposes to assess the health economic consequences of macrosomia. Based on international epidemiological and US population costing data, it was shown that the budget impact related to short term obstetric complications for both mother and child is considerable. The presented model offers a first approach for further health technology assessments in different parts of the world and can be used with country specific data to evaluate cost-effectiveness of proposed preventive interventions to reduce the current and future public health consequences of macrosomia. It is anticipated that the reported pilot assessment using available US costing data provides a conservative picture of the true health economic impact of macrosomic births, given the reported increase in maternal overweight and obesity, not only in developed but also in developing countries. The recent debate on diagnostic criteria for GDM stirred by the linear relationship between maternal hyperglycemia and fetal outcomes adds further fuel to this assumption.[31,33]

Relevance and applicability of this framework

Maternal BMI, nutritional status and dietary intake are the main determinants of fetal growth as well the occurrence of maternal hyperglycemia. The latter may result in GDM, defined as diabetes first diagnosed during pregnancy, and is particularly prevalent –and

increasing rapidly– in the Asian regions[29]. Ethnic differences play a pivotal role in the risk for fetal macrosomia. Worldwide, the rising epidemics of overweight in girls and women of child-bearing age do not bode well and calls for preventive strategies.[52]

A limitation of this modelling approach lies in the lack of randomized trial evidence on targeted lifestyle interventions in pregnancy and their effect on birth outcomes.[53,54] However, as maternal overweight, excessive GWG by itself, GDM and elevated fasting plasma glucose levels during pregnancy have all been reported to be significant risk factors for macrosomia,[9,18,20,21] it seems reasonable to assume that a reduction of GDM (severity) and obese pregnancies would lead to fewer complications and thus decrease the related health care costs. Another limitation of the presented framework is its restriction to short-term costs only. More and more evidence is emerging on the increased long-term risks for macrosomic babies to develop future health concerns, including metabolic syndrome, diabetes and cancer. Besides the further increase of related health care expenditures, this also raises the question of the impact on the next generations,[55,56] which argues in favor of implementing health strategies that may contribute to prevent a vicious circle of NCD.

Dietary management and exercise are potentially effective interventions to prevent excessive weight gain and GDM if measures are established before or in the early stages of pregnancy.[57] Evidence from observational studies and clinical trials indicates that dietary energy intake and the source of energy influences glucose metabolism and insulin responses.[58,59] High fat diets, likely to be unbalanced in their macronutrient composition, have been demonstrated to increase the risk for GDM recurrence in future pregnancies.[60] An evaluation of pregnancy management in women with GDM or gestational mild hyperglycemia in France demonstrated that there were no LGA babies in women whose carbohydrate intake was at least 210 g/day indicating the significance of sufficient carbohydrate intake during pregnancy.[61] The study suggested that nutrition counseling should be directed at an adequate carbohydrate intake of 250 g/day, while maintaining a low fat diet to limit the total energy intake. Indeed, higher consumption of saturated fat and *trans*-fat as a percentage of total energy intake, added sugar and lower intake of vegetables and fruit fiber during the second trimester of pregnancy were associated with greater risk for glucose intolerance during the last trimester of pregnancy.[62] A similar study suggests an association between saturated fat and sugar intake during the second trimester with not only birth weight, but also body weight and adiposity in the offspring at 5 years of age.[63] A 'high' glycemic diet resulting in elevated postprandial glucose levels compared to a 'low' glycemic diet may significantly increase birth weight in healthy pregnant women.[64,65] Although these studies suggest that a balanced macronutrient intake as well as carbohydrate quality play a crucial role in

dietary management of GDM, health economic costs assessment of dietary approaches to date is limited.

Long-term risk of gestational diabetes mellitus

The current pilot analysis focusses only on costs related to perinatal complications of macrosomic birth. Several studies on the association between GDM and long-term risk of diabetes mellitus show that women with GDM also have a greater risk of developing diabetes in the future compared to pregnant women with a normal glucose tolerance.[31,66]

A review by Henry and Beischer provides similar results.[67] Using life table techniques, seventeen years after the initial diagnosis of GDM, 40% of women were diabetic compared with 10% in a matched control group of women who had normal glucose tolerance in pregnancy. The incidence of diabetes was higher among women who were older, more obese, of greater parity and with more severe degrees of glucose intolerance during pregnancy. Diabetes also occurred more commonly among women who had a first-degree relative who was diabetic, in women born in Mediterranean and East Asian countries, and in those who had GDM in two or more pregnancies. Despite differing testing techniques and varying criteria for the diagnosis of GDM, follow-up studies from across the world consistently showed a higher rate of subsequent diabetes among GDM mothers, associated with increased morbidity and a higher mortality rate. Costs associated with the health of the mother in later years were not considered in the current model and recent epidemiologic data suggest that the real costs of macrosomic birth are considerable higher than presented in this manuscript.

Long term risks of macrosomia

Fetal macrosomia is a risk factor for the development of obesity in childhood. In the European cohort IDEFICS, children who were macrosomic at birth showed significantly higher actual values of BMI, waist circumference, and sum of skin fold thickness.[68]

A recent prospective study, conducted in China, examined the risk factors and long-term health consequences of macrosomia.[69] Using a population sample of 21 315 mother-child pairs, the children were prospectively followed and assessed for obesity seven years after birth. Macrosomic infants showed an increased susceptibility to develop childhood overweight and/or obesity. Obesity among children is a significant risk factor for the development of insulin resistance, and the degree of obesity is correlated with the degree of insulin resistance.[70,71] A recent literature review indicates an extra lifetime medical cost of $19 000 for the obese child compared to a normal weight child, in the USA. To put this into perspective, if multiplied with the number of obese 10-year-olds today this yields a total direct medical cost of obesity of roughly $14 billion for this age alone.[72]

To investigate the relationship between birth weight and later development of GDM, a retrospective study on the medical records of 388 women from Malta, diagnosed for GDM demonstrated that high birth weight is an important correlate for the subsequent development of GDM in later life.[73] This study further supports the notion that the intrauterine influences on pancreatic development and peripheral response to insulin contribute to the development of adult-onset of T2DM.

Boney examined the development of metabolic syndrome among LGA and appropriate-for-gestational age children.[74] They observed that obesity among 11-years-old children was a strong predictor for insulin resistance, and the combination of LGA status and a mother with GDM might increase this risk. They also reported that LGA offspring of diabetic mothers were at significant risk of developing metabolic syndrome in childhood.

Again, costs associated with the health of the offspring in later years were not considered in the current model and the above-mentioned observations further support the notion that the real costs of macrosomic births are considerably higher than the outcomes presented in this pilot analysis.

CONCLUSION

The health economic decision tree as reported in this paper, allows mapping the short-term care burden and public health impact of complications resulting from GDM and overweight pregnancies. This model gives an impulse for further assessment of the cost-effectiveness of preventive interventions. In addition, as the incidence of macrosomia and related risk-factors will be a key driver for future health care costs, exploration of the most appropriate data sources and assumptions, as well as additional data obtained from longitudinal studies and other epidemiologic recordings, are required to evaluate the long-term consequences.

The current budget impact analysis, using available USA data and on short-term costs only, shows that the annual budget impact of GDM and pregnancy overweight resulting in macrosomic birth can be substantial, thus emphasizing the importance of avoiding these adverse health outcomes.

The reported differences on GDM incidence, obesity or the combination thereof, as well as the predisposition in people of Asian ethnicity to develop diabetes and the high proportion of undiagnosed diabetic conditions in this part of the world, stresses the

need to collect more country-specific data for improving the assessments of the health economic burden of macrosomic birth and of its later consequences.

The difficulties to change lifestyle and dietary behavior are generally recognized, however the (pre)pregnancy period offers a window of opportunity for healthcare monitoring and nutritional and lifestyle interventions in the receptive population of future parents. Well-targeted educational programs on lifestyle and food behavior during (pre)pregnancy are likely to improve adverse birth outcomes related to macrosomia. On the long run, this might represent a valuable contribution to the global efforts in the fight against NCD.

REFERENCES

1 Morton SB. (2006) Maternal nutrition and fetal growth and development. In: Gluckman PD and Hanson MA (eds). Developmental Origins of Health and Disease. Cambridge University Press. Cambridge UK, pp. 98-129.

2 Black RE, Allen LH, Bhutta ZA, *et al*. (2008) Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* 371, 243–260.

3 Johnson RC, Schoeni RF. (2011) The Influence of Early-Life Events on Human Capital, Health Status, and Labor Market Outcomes Over the Life Course. *B E J Econom Anal Policy* 11(3), 2521. doi:10.2202/1935-1682.2521

4 Boulet SL, Alexander GR, Salihu HM, Pass M. (2003) Macrosomic births in the United States: determinants, outcomes, and proposed grades of risk. *Am J Obstet Gynecol.* 188, 1372-8.

5 Costa BM,. Paulinelli RR, Barbosa MA. (2012) Association between maternal and fetal weight gain: cohort study. *Sao Paulo Med J*. 130, 242-247.

6 de Oliveira LC, Pacheco AH, Rodrigues PL, Schlüssel MM, Spyrides MH, Kac G. (2008) Factors accountable for macrosomia incidence in a study with mothers and progeny attended at a Basic Unity of Health in Rio de Janeiro, Brazil. *Rev Bras Ginecol Obstet.* 30, 486-93.

7 Kac G, Velasquez-Melendez G. (2005) Gestational weight gain and macrosomia in a cohort of mothers and their children. *J Pediatr. (Rio J)* 81, 47-53.

8 Rodrigues S., Robinson EJ, Kramer MS, Gray-Donald K. (2000) High rates of infant macrosomia: a comparison of a Canadian native and a non-native population. *J Nutr*. 130, 806-12.

9 Shi P, Yang W, Yu Q, Zhao Q, Li C, Ma X *et al*. (2014) Overweight, gestational weight gain and elevated fasting plasma glucose and their association with macrosomia in chinese pregnant women. *Matern Child Health J*. 18, 10-15.

10 Koyanagi A1, Zhang J, Dagvadorj A, Hirayama F, Shibuya K, Souza JP, Gülmezoglu AM. (2013) Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. *Lancet* 381, 476-83.

11 Henriksen T. (2008) The macrosomic fetus: a challenge in current obstetrics. *Acta Obstet Gynecol Scand*. 87, 134-145.

12 Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. HAPO Study Cooperative Research Group. (2008) Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 358, 1991-2002.

13 Jastrow N, Roberge S, Gauthier RJ, Laroche L, Duperron L, Brassard N, *et a*l. (2010) Effect of birth weight on adverse obstetric outcomes in vaginal birth after cesarean delivery. *Obstet Gynecol*. 115(2 Pt 1), 338–343.

14 Robinson H, Tkatch S, Mayes DC, Bott N, Okun N. (2003) Is maternal obesity a predictor of shoulder dystocia? *Obstet Gynecol*. 101, 24-27.

15 Kawai M, K. Kishi K. (1999) Adaptation of pancreatic islet B-cells during the last third of pregnancy: regulation of B-cell function and proliferation by lactogenic hormones in rats. *Eur J Endocrinol*. 141, 419-425.

16 Parsons JA, Brelje TC, Sorenson RL. (1992) Adaptation of islets of Langerhans to pregnancy: increased islet cell proliferation and insulin secretion correlates with the onset of placental lactogen secretion. *Endocrinology* 130, 1459-1466.

17 Clapp JF. (2006) Effects of diet and exercise on insulin resistance during pregnancy. *Metabolic Syndrome and Related Disorders* 4, 84–90.

18 Li N, Liu E, Guo J, Pan L, Li B, Wang P, *et al*. (2013) Maternal prepregnancy body mass index and gestational weight gain on pregnancy outcomes. *PLoS One* 8, e82310.
19 Bodnar LM, Siega-Riz AM, Simhan HN, Diesel JC, Abrams B. (2010) The impact of exposure misclassification on associations between prepregnancy BMI and adverse pregnancy outcomes. *Obesity (Silver Spring)* 18, 2184-2190.
20 Black MH, Sacks DA, Xiang AH, Lawrence JM. (2013) The Relative Contribution of Prepregnancy Overweight and Obesity, Gestational Weight Gain, and IADPSG-Defined Gestational Diabetes Mellitus to Fetal Overgrowth. *Diabetes Care* 36, 56-62.
21 Liu Y, Dai W, Dai X, Li Z. (2012) Prepregnancy body mass index and gestational weight gain with the outcome of pregnancy: a 13-year study of 292,568 cases in China. *Arch Gynecol Obstet*. 286, 905-911.
22 Institute of Medicine/National Research Council (Committee to Reexamine IOM Pregnancy Weight Guidelines, F.a.N.B.a.B.o.C., Youth, and Families). (2009) Weight gain during pregnancy: reexamining the guidelines., Institute of Medicine (eds): Washington, DC.
23 Tanvig M, Wehberg S, Vinter CA, Joergensen JS, Ovesen PG, Beck-Nielsen H, Jensen DM, Christesen HT. (2013) Pregestational body mass index is related to neonatal abdominal circumference at birth-a Danish population-based study. *BJOG* 120, 320-330.
24 Egan AM, Dennedy MC, Al-Ramli W, Heerey A, Avalos G, Dunne F. (2014) ATLANTIC-DIP: excessive gestational weight gain and pregnancy outcomes in women with gestational or pregestational diabetes mellitus. *J Clin Endocrinol Metab*. 99, 212-219.
25 Poston L, Harthoorn LF, Van Der Beek EM. (2011) Obesity in pregnancy: implications for the mother and lifelong health of the child. A consensus statement. *Pediatr Res*. 69, 175-180.
26 Vaag A, Brøns C, Gillberg L, Hansen NS, Hjort L, Arora GP, Nihal Thomas, *et al*. (2014) Genetic, nongenetic and epigenetic risk determinants in developmental programming of type 2 diabetes. *Acta Obstet Gynecol Scand*. 93(11), 1099–1108.
27 Beischer NA, Oats JN, Henry OA, Sheedy MT, Walstab JE. (1991) Incidence and severity of gestational diabetes mellitus according to country of birth in women living in Australia. *Diabetes* 40 (Suppl 2), 35-38.
28 Ferrara A, Kahn HS, Quesenberry CP, Riley C, Hedderson MM. (2004) An increase in the incidence of gestational diabetes mellitus: Northern California, 1991-2000. *Obstet Gynecol*. 103, 526-533.
29 Hunsberger M, Rosenberg KD, Donatelle RJ. (2010) Racial/ethnic disparities in gestational diabetes mellitus: findings from a population-based survey. *Womens Health Issues* 20, 323-328.
30 Rosenberg TJ, Garbers S, Lipkind H, Chiasson MA. (2005) Maternal obesity and diabetes as risk factors for adverse pregnancy outcomes: differences among 4 racial/ethnic groups. *Am J Public Health* 95, 1545-1551.
31 Jiwani A, Marseille E, Lohse N, Damm P, Hod M, Kahn JG. (2012) Gestational diabetes mellitus: results from a survey of country prevalence and practices. *J Matern Fetal Neonatal Med*. 25, 600-10.
32 Zawiejska A, Wender-Ozegowska E, Radzicka S, Brazert J. (2014) Maternal hyperglycemia according to IADPSG criteria as a predictor of perinatal complications in women with gestational diabetes: a retrospective observational study. *J Matern Fetal Neonatal Med*. 27, 1526–1530.
33 Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, Metzger BE, *et al*. (2012) Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel–recommended criteria. *Diabetes Care* 35, 526–528. doi:10.2337/dc11-1641
34 Ma RCW, Chan JCN. (2008) Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann. N.Y. Acad. Sci.* 1281, 64–91.

35 Weinstein MC, Fineberg HV. (1980) Clinical Decision Analysis. WB Saunders Co (eds), Philadelphia, PA, pp 228-265.
36 Lenoir-Wijnkoop I, Dapoigny M, Dubois D, van Ganse E, Gutierrez-Ibarluzea I, J. Hutton J, *et al*. (2011) Nutrition economics – characterising the economic and health impact of nutrition. *Br J Nutr*. 105: 157–166.
37 Lampe K, Mäkelä M, Garrido MV, Anttila H, Autti-Rämö I, Hicks NJ, *et al*. (2009) European network for Health Technology Assessment (EUnetHTA). The HTA core model: a novel method for producing and reporting health technology assessments. *Int J Technol Assess Health Care* 25 (Suppl 2), 9-20.
38 Michlin R, Oettinger M, Odeh M, Khoury S, Ophir E, Barak M, *et al*. (2000) Maternal obesity and pregnancy outcome. *Isr Med Assoc J*. 2, 10-3.
39 Salihu HM, Weldeselasse HE, Rao K, Marty PJ, Whiteman VE. (2011) The impact of obesity on maternal morbidity and feto-infant outcomes among macrosomic infants. *J Matern Fetal Neonatal Med*. 24, 1088-94.
40 Pathi A, Esen U, Hildreth A. (2006) A comparison of complications of pregnancy and delivery in morbidly obese and non-obese women. *J Obstet Gynaecol*. 26, 527-30.
41 Galtier-Dereure F, Montpeyroux F, Boulot P, Bringer J, Jaffiol C. (1995) Weight excess before pregnancy: complications and cost. *Int J Obes Relat Metab Disord*. 19, 443-448.
42 Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, *et al*. (2009) Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med*. 361, 1339-1348.
43 Ohno MS, Sparks TN, Cheng YW, Caughey AB. (2011) Treating mild gestational diabetes mellitus: a cost-effectiveness analysis. *Am J Obstet Gynecol*. 205, 282.e1-7.
44 Mission JF, Ohno MS, Cheng YW, Caughey AB. (2012) Gestational diabetes screening with the new IADPSG guidelines: a cost-effectiveness analysis. *Am J Obstet Gynecol*. 207, 326.e1-9.
45 Reece EA. (2010) The fetal and maternal consequences of gestational diabetes mellitus. *J Matern Fetal Neonatal Med*. 23, 199-203.
46 Keshavarz M, Cheung NW, Babaee GR, Moghadam HK, Ajami ME, Shariati M. (2005) Gestational diabetes in Iran: incidence, risk factors and pregnancy outcomes. *Diabetes Res Clin Pract*. 69, 279-286.
47 Horvath K, Koch K, Jeitler K, Matyas E, Bender R, Bastian H *et al*. (2010) Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. *BMJ* 340, c1395. doi:10.1136/ bmj.c1395
48 Langer O, Yogev Y, Most O, Xenakis EM. (2005) Gestational diabetes: the consequences of not treating. *Am J Obstet Gynecol*. 192, 989-997.
49 Herbst MA. (2005) Treatment of suspected fetal macrosomia: a cost-effectiveness analysis. *Am J Obstet Gynecol*. 193(3 Pt 2), 1035-1039.
50 Mitanchez D. (2010) Foetal and neonatal complications in gestational diabetes: perinatal mortality, congenital malformations, macrosomia, shoulder dystocia, birth injuries, neonatal complications. *Diabetes Metab*. 36(6 Pt 2), 617-627.
51 http://www.indexmundi.com/g/g.aspx?v=21&c=us&l=en. Accessed 26 July 2014
52 Mulla WR, Henry TQ, Homko CJ. Gestational diabetes screening after HAPO: has anything changed? (2010) *Current Diabetes Reports* 10:224–228.

53 Briley AL, Barr S, Badge S, Bell R, Croker H, Godfrey KM, *et a*l. (2014) A complex intervention to improve pregnancy outcome in obese women; the UPBEAT randomised controlled trial. *BMC Pregnancy and Childbirth* 14, 74.
54 Balaji V, Balaji MS, Datta M, Rajendran R, Kragelund Nielsen K, Radhakrishnan R,Kapur A, Seshiah V. (2014) A cohort study of gestational diabetes mellitus and complimentary qualitative research: background, aims and design. *BMC Pregnancy and Childbirth* 14, 378.
55 Roseboom TJ, Watson ED. (2012) The next generation of disease risk: are the effects of prenatal nutrition transmitted across generations? Evidence from animal and human studies *Placenta* 33 Suppl 2, e40-4. doi:10.1016/j.placenta.2012.07.018.
56 Catalano PM. (2003) Obesity and Pregnancy—The Propagation of a Viscous Cycle? *J Clin Endocrinol Metab*. 88(8), 3505–3506.
57 Thangaratinam S, Rogozińska E, Jolly K, Glinkowski S, Duda W, Borowiack E, *et al*. (2012) Interventions to reduce or prevent obesity in pregnant women: a systematic review. *Health Technol Assess*. 16(31), iii-iv, 1-191.doi:10.3310/hta16310.
58 Hu, FB, van Dam RM, Liu, S. (2001) Diet and risk of Type II diabetes: the role of types of fat and carbohydrate. *Diabetologia* 44, 805-17.
59 Galgani, JG, Uauy RD, Aguirre CA, Dıaz EO. (2008) Effect of the dietary fat quality on insulin sensitivity. *Br J Nutr*. 100, 471-479.
60 Moses RG, Shand JL, Tapsell LC. (1997) The recurrence of gestational diabetes: could dietary differences in fat intake be an explanation? *Diabetes Care* 20, 1647-50.
61 Romon M, Nuttens MC, Vambergue A, Vérier-Mine O, Biausque S, Lemaire C, *et al*. (2001) Higher carbohydrate intake is associated with decreased incidence of newborn macrosomia in women with gestational diabetes. *J Am Diet Assoc*. 101, 897-902.
62 Ley SH, Hanley AJ, Retnakaran R, Sermer M, Zinman B, O'Connor DL. (2011) Effect of macronutrient intake during the second trimester on glucose metabolism later in pregnancy. *Am J Clin Nutr*. 94, 1232-1240.
63 Murrin C, Shrivastava A, Kelleher CC. (2013) Maternal macronutrient intake during pregnancy and 5 years postpartum and associations with child weight status aged five. *Eur J Clin Nutr*. 67, 670–679.
64 McGowan CA, McAuliffe FM. (2010) The influence of maternal glycaemia and dietary glycaemic index on pregnancy outcome in healthy mothers. *Br J Nutr*. 104, 153-159.
65 Tzanetakou IP, Mikhailidis DP, Perrea DN. (2011) Nutrition during pregnancy and the effect of carbohydrates on the offspring's metabolic profile: In search of the "Perfect Maternal Diet". *Open Cardiovasc Med*. 5, 103-109.
66 Bellamy L, Casas JP, Hingorani AD, Williams D. (2009) Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 373, 1173–1179.
67 Henry OA, Beischer NA. (1991) Long-term implications of gestational diabetes for the mother. *Baillieres Clin Obstet Gynaecol*. 5, 461-83.
68 Sparano S, Ahrens W, De Henauw S, Marild S, Molnar D, Moreno LA, *et al*. (2013) Being macrosomic at birth is an independent predictor of overweight in children: results from the IDEFICS study. *Matern Child Health J*. 17, 1373-1381.
69 Gu S, An X, Fang L, Zhang X, Zhang C, Wang J, *et al*. (2012) Risk factors and long-term health consequences of macrosomia: a prospective study in Jiangsu Province, China. *J Biomed Res*. 26, 235-240.
70 Arslanian S, Suprasongsin C. (1996) Insulin sensitivity, lipids, and body composition in childhood: is syndrome X present? *J Clin Endocrinol Metab*. 81, 1058–1062.

71 Young-Hyman D, Schlundt D, Herman L, DeLuca F, Counts D. (2001) Evaluation of the insulin resistance syndrome in 5-to-10-year old overweight/obese African-American children. *Diabetes Care* 24, 1359–1364.

72 Finkelstein EA, Graham WCK, Malhotra R. (2014) Lifetime Direct Medical Costs of Childhood Obesity. *Pediatrics* 133, 1–9.

73 Savona-Ventura C, Chircop M. (2003) Birth weight influence on the subsequent development of gestational diabetes mellitus. *Acta Diabetol*. 40, 101-104.

74 Boney CM, Verma A, Tucker R, Vohr BR. (2005) Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics* 115, e290-6.

Chapter 8

An economic model for the use of yoghurt in type 2 diabetes risk reduction in the UK

Irene Lenoir-Wijnkoop, James Mahon, Lindsay Claxton, Alicia Wooding, Andrew Prentice, Nick Finer

Published in: BMC Nutr. 2016;2, 77

ABSTRACT

Background In the UK, diabetes accounts for approximately 10% of the total UK National Health Service (NHS) resource expenditure, a figure that has been predicted to increase to 17% by 2035/2036. Meta-analysis of association studies indicate that yogurt consumption is potentially protective against type 2 diabetes (T2D). The purpose of this study was to explore the potential economic benefit to the UK NHS of a population increase in yoghurt consumption as a preventative measure against development of T2D.

Methods A patient simulation model was constructed for adults in the UK over the age of 25 years old using incidence rates for developing T2D with both current and increased yoghurt consumption. The reduction in risk in developing T2D associated with higher yoghurt consumption was taken from a meta-analysis of studies of dairy consumption on T2D risk. In each annual cycle of the model a patient could develop complications and comorbidities that are known to be more common in patients with T2D. Incidence rates for these conditions for diabetics and non-diabetics were taken from published studies. The model had a 25 year time horizon.

Results The model predicts that increasing average yoghurt consumption by adults over 25 years of age in the UK by 100g daily could result in 388,000 fewer people developing T2D over 25 years. This could save the UK NHS £2.3bn in direct T2D treatment costs and the costs of treating T2D associated complications. In addition, 267,000 QALYs would be generated. If the NHS values a QALY valued at £20,000, this would mean that the NHS would be prepared to pay £5.5bn for an intervention that generated the same number of QALYs.

Conclusions Increasing yoghurt consumption in the adult population of the UK by 100g per day could generate substantial cost savings to the NHS as well as significant patient benefit through reductions in the incidence of T2D.

BACKGROUND

The prevalence of type 2 diabetes (T2D) is rapidly rising and now affects 9% of the global population[1] and is projected to be the seventh leading cause of death by 2030.[2] Between 2010 and 2030, the prevalence of diabetes has been forecast to increase by 20% in developed countries and 69% in developing counties.[3] In 2015, the costs of diabetes and related complications accounted for 12% of global healthcare budgets, or between USD673 billion and USD1,197 billion.[4] Lifestyle interventions can prevent or delay some cases of T2D and thus reduce the huge economic burden of diabetes.[5] There is an increasing focus on pinpointing food groups that can be used to reduce chronic conditions, and evidence is emerging that dairy products may play an important role in metabolic disease and T2D prevention and management.[6] Dairy products are an important source of protein, fats, vitamins and minerals, but many also contain a proportion of saturated fatty acids (SFA)[7] which are commonly thought to have a negative effect on cardiometabolic health.[8] However, recent investigations indicate that some types of SFA may actually be beneficial to T2D management; for example, myristic acid has been associated with improved glucose homeostasis,[9,10] and plasma levels of very long-chain SFA were inversely correlated with T2D incidence in the EPIC-InterAct case-cohort study.[11] This may explain why daily consumption of yoghurt has also been linked, in a large meta-analysis, to a lower risk of developing T2D, an association that was not seen for general dairy consumption, suggesting that the nutritional composition of yoghurt may have specific benefits in diabetes prevention.[12]

In the UK, diabetes accounts for approximately 10% of the total UK National Health Service (NHS) resource expenditure, a figure that has been predicted to increase up to 17% by 2035/2036 with 80% of this cost as a result of complications.[13] Previous econometric research has highlighted the potential cost effectiveness of dietary interventions to prevent or delay the onset of T2D. “The Mediterranean Diet” and the “Intensive Lifestyle Change to Prevent Diabetes” have been cited as highly cost-effective interventions gaining £410 and £750 per QALY respectively.[14] The American Diabetes Association (ADA) recommend several interventions for preventing and treating T2D; a systematic review from 2010 indicated that preventative interventions were the most cost-effective, with the strongest evidence available for “primary prevention through lifestyle modification”.[15] The purpose of this study was to explore the potential economic benefit to the UK of an increase in yoghurt consumption as a preventative measure against development of T2D.

METHODS

The primary research question was: How would an increase in the average consumption of conventional yoghurt impact upon UK health care expenditure in the management and treatment of T2D? A supplementary research question was: How would an increase in the average consumption of conventional yoghurt impact upon the quality and length of life for a UK population, based on cases of T2D avoided or delayed?

The model

The patient pathway is shown in Figure 1 and was used to build a patient simulation model in Microsoft Excel. To summarise the pathway, a virtual subject enters the model with randomly assigned characteristics (age, gender, pre-existing conditions). If he/she does not already have T2D, the risk of developing the disease in each subsequent year is reduced by higher yoghurt consumption. In the model, each year a subject can develop one or several complications, or die; for a subject who already has T2D, the probability of developing a complication is increased.

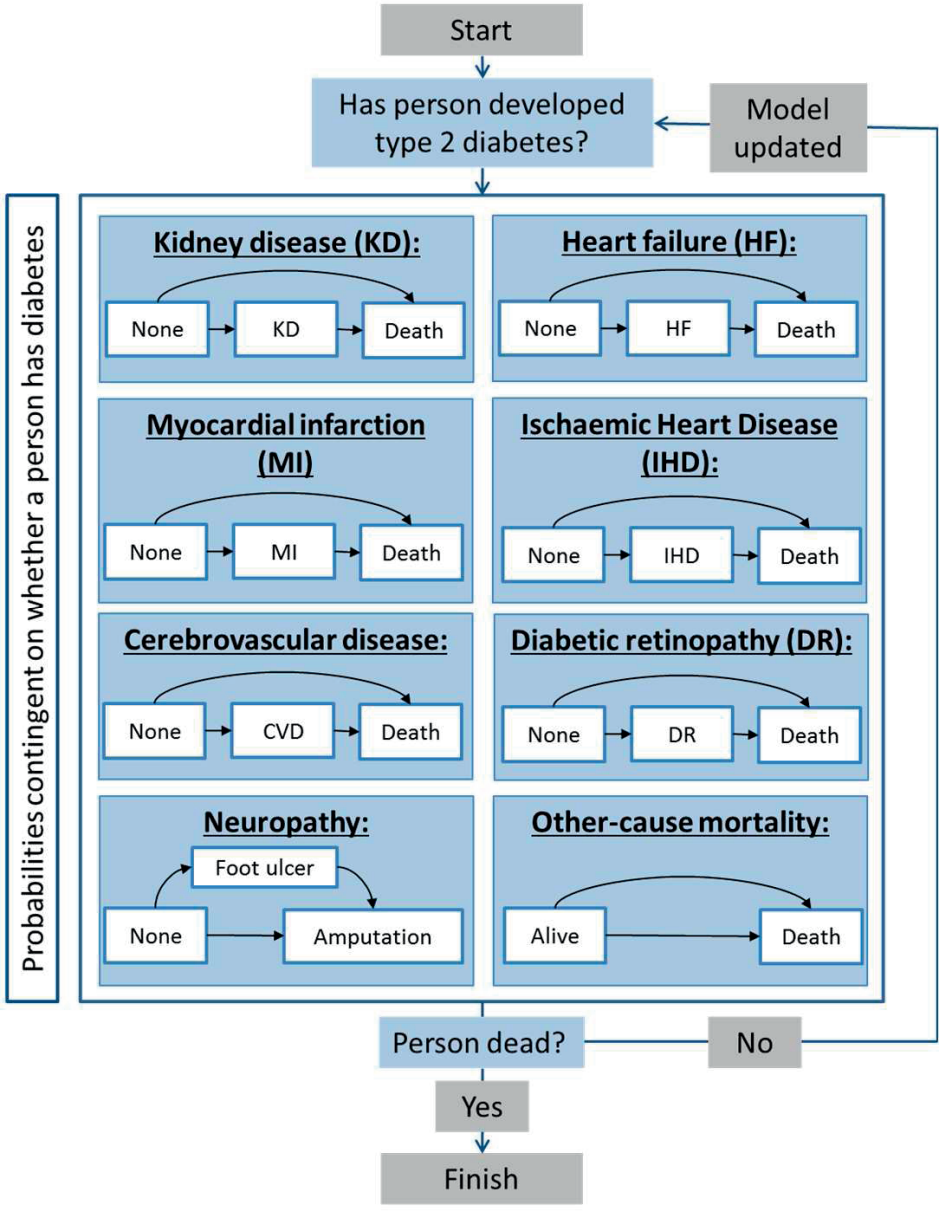
The modelled population was all people in the UK aged over 25 years. Age and gender distributions were taken from the Office for National Statistics (ONS) population pyramid projections.[16]

Effectiveness

Effectiveness was derived from Chen *et al.,*[12] a large study, combining 14 prospective cohorts and a total of 459,790 individuals, with 35,863 developing T2D within 4 million patient-years of follow-up. Based upon a correlation between yoghurt consumption and developing T2D, Chen estimated that for each additional serving of 244g of yoghurt, the relative risk (RR) of developing T2D is 0.82. To undertake our modelling, we assumed that the relationship was causative and that the risk reduction occurs linearly with changes in yoghurt consumption and adjusted for current average yoghurt consumption in the UK of 20.4g per person per day.[17] In the base case model it was assumed that average daily consumption would rise by 100g to 125g (a standard size single serving 'pot' in the UK). This equated to a change in the RR of developing T2D from 0.99 at current consumption, to 0.91 if average consumption increased to 125g daily.

The RRs were estimated using a linear interpolation between the RR associated with no daily yoghurt consumption (0g, RR = 1), and the RR associated with a daily serving (244g, RR = 0.82).

Figure 1. Patient pathway



Costs

Throughout the model we have taken a conservative approach. Costs incorporated into the model are considered in 3 categories: direct diabetes management costs; hospital; and non-inpatient costs for treating diabetes-related complications.

Diabetes management costs were taken from Hex *et al*.,[13] who reported a mean direct treatment cost (including diabetic medications, primary care visits, retinopathy screening, influenza vaccination and medical examinations) of £513.54 per person with diabetes to the UK NHS.

For treatment of complications, costs and resource use were modelled using a recently published logit model that looked at the UKPDS data on healthcare costs.[18] Costs included those for all admissions and inpatient procedures as well as outpatient consultations with GPs, nurses, health visitors, dieticians, chiropodists and eye care specialists. Whether a condition required initial hospitalisation and/or annual on-going treatment post discharge was modelled through a random drawing of the logit model. Parameters of the logit model are summarized in Table 1.

Table 1. Logit model values of costs associated with treating complications of T2D

	Variable	Logit model coefficient	Hospital care (£)	Non-patient care (£)	Additional (£)
	Constant	−1.353	3318	531	-
	Aged 65+	0.041	38	4	-
	Male	−0.118	−218	−162	-
Event during current year	Ischaemic heart disease (angina)	3.379	8636	331	-
	Fatal Ischaemic heart disease	4.701	1037	-	-
	Heart failure	2.98	1147	447	-
	Fatal heart failure	-	-	-	3637
	Myocardial infarction	4.506	3845	963	-
	Fatal myocardial infarction	5.115	−1341	-	-
	CKD requiring RRT	-	-	-	23275
	Stroke	2.419	7133	559	-
	Fatal stroke	-	1042	-	-
	Diabetic retinopathy	-	-	-	138
	Blindness in one eye	0.825	1621	1258	-
	Foot ulcer	-	-	-	743.68
	Amputation	4.059	7516	2166	-
Historic event	Ischaemic heart disease (angina)	0.553	2042	121	-
	Heart failure	0.824	2017	441	-
	Myocardial infarction	0.68	1369	671	-
	Stroke	0.37	2371	224	-
	Blindness in one eye	0.266	−601	205	-
	Amputation	1.254	1616	1079	-

The model conservatively considered that the probability of experiencing a particular event, or developing a condition, was independent of the presence of others. However, the costs that could be incurred when an event or condition arises could be dependent on the presence of other conditions. For example, having a stroke would not make it more likely a person had a myocardial infarction (MI) in the future but it would make it more likely that an MI would lead to hospitalisation. Other than for foot ulcers (which were considered as a one off certainty of the cost of the event), only the first event of each complication was considered in the model.

Specific additional costs were also identified to complete the necessary inputs into the model:

- Heart failure and diabetic retinopathy – derived in Sheffield Diabetes model (SDM) from older UKPDS data;[19]
- CKD – derived in SDM from NHS reference costs;[20]
- Foot ulcer – NHS diabetic foot care report.[21]

Quality of Life

At the end of each cycle a person exists in an age and disease specific health state. Each health state has an associated level of quality of life that is measured via utility estimates from the literature. With the exception of amputation, all utility values were derived from Sullivan[22] that estimated health states from 80,000 people in the USA and applied UK utility weights to these health states. For lower limb amputation, a utility value was taken from Bagust.[23]

The age and disease utility decrements used in the model are given in Table 2. For cardiovascular conditions, the maximum decrement of the three possible conditions in the model was applied if more than one of the conditions was experienced.

Once a condition is experienced, that utility decrement exists for the remainder of the patient's life (with the exception of foot ulcers). It is noted that the utility value is an average value of people with both good and poor outcomes after events.

Table 2. Utility decrements applied in the model

Condition	Decrement
Age (per year)	−0.00029
Diabetes	−0.07
Ischemic heart disease	−0.09
Heart failure	−0.12
Myocardial infarction	−0.06
CKD requiring RRT	−0.11
Cerebrovascular disease (stroke)	−0.10
Diabetic retinopathy	−0.04
Blindness	−0.06
Foot ulcer	−0.07
Amputation	−0.11

Disease incidence and prevalence rates

Age specific prevalence rates of T2D and age and gender specific prevalence rates of related comorbidities were required to be able to estimate the likelihood of an individual entering the model, already having T2D or an associated comorbidity (with or without the presence of T2D). Similarly, age related incidence rates were required to move people through the model during each annual cycle. The source of each of the incidence and prevalence rates is shown in Table 3.

Table 3. Model disease incidence and prevalence rates

Condition	Prevalence source	Incidence source
Diabetes (Type 2)	Scottish Diabetes Survey 2013 [31]	Scottish Diabetes Survey 2013 [31]
Ischemic heart disease	British Heart Foundation 2012 [32]	British Heart Foundation 2012 [32]
Heart failure	Welsh Health Survey 2010 [33]	British Heart Foundation 2012 [32]
Myocardial infarction	British Heart Foundation 2012 [32]	British Heart Foundation 2012 [32]
Renal replacement therapy (RRT)	The Renal Registry 2012 [34]	EUGLOREH [35]
Cerebrovascular disease (stroke)	British Heart Foundation 2012 [32]	Oxford Vascular study [36]
Diabetic retinopathy	Zhang et al. (2010) [37]	DARTS diabetes register McAlpine et al. (2005) [38]
Blindness	Prasad et al. (2001) [39]	Trautner et al. (2003) [40]
Neuropathy	Abbott et al. (2001) [41]	Abbott et al. (2002) [41]
Lower limb amputation	Ahmad et al. (2014) [42]	Johannesson et al. (2009) [43]

Relative risks of comorbid disease with T2D

The National Diabetes Audit 2011-2012 provided data on the relative increase in the risk of comorbid disease for people with T2D.[24] The audit recorded data from 2.5 million people in England and Wales. The increase in risk for each condition is shown in Table 4.

Table 4. Increase in risk of conditions with T2D

Disease	Increase in risk
Ischemic heart disease	76%
Heart failure	73%
Myocardial infarction	55%
RRT	64%
Cerebrovascular disease (stroke)	34%
Lower limb amputation	287%

Mortality

Mortality occurs in the model in two distinct ways; a person may die from developing a particular condition or event, such as cerebrovascular disease (stroke) or MI; or a person may suffer an 'all-other cause death' based upon age and gender derived all-cause mortality data. Individual condition/event mortality rates were taken from published sources shown in Table 5 and all other cause mortality was sourced from the ONS.[16]

Table 5. Source of mortality rates

Disease	Source
Ischemic heart disease	NICE CG108. (2006) [44]
Heart failure, year one	Cowie et al. (2000) [45]
Heart failure, after year one	Hobbs et al. (2007) [46]
Myocardial infarction	British Heart Foundation 2012 [32]
RRT	The Renal Registry 2012 [34]
Cerebrovascular disease (stroke)	British Heart Foundation 2012 [32]

RESULTS

Results under the base case assumptions for 100,000 individuals cycled through the model were generated. The average individual and total (extrapolated to all people in the UK over 25) cost savings and QALY gains from higher yoghurt consumption are shown in Tables 6 and 7.

The base case results – which are based on a conservative approach to modelling potential benefits - show that if the average consumption of yoghurt in the UK for people over the age of 25 increased from 20.4g to a 125g serving, discounted mean savings over five years to the NHS from reducing the rate of T2D and T2D related complications would be £3.21 (95%CI: £2.65, £3.77) per person. This saving would increase each year up to and including the 25 years considered in the model. By 25 years the saving per person from increased yoghurt consumption would be £54.35 (£49.87, £58.82).

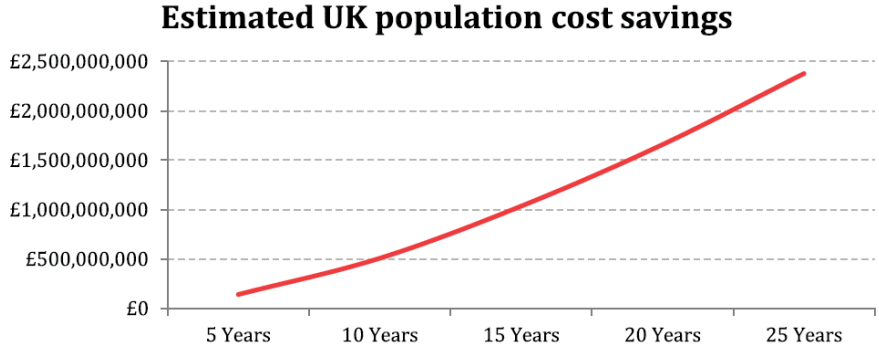
Applying the average saving to the UK population over the age of 25 would generate total discounted savings to the NHS of approximately £140 million (£116m, £165m) over five years that would increase to £2,377 million (£2,181m, £2,573m) over 25 years if average consumption increased to 125g.

From a quality-of-life perspective, if the average consumption of yoghurt by people over 25 in the UK increased to 125g per day, an average additional 0.0004 discounted QALYs (0.0003, 0.0005) per person over five years would be generated; this would increase to an additional 0.0063 discounted QALYs (0.0056 to 0.0070) after 25 years. At a population level this would generate approximately 276,352 (246,172, 306,532) total additional discounted QALYs over 25 years. If these QALYs were valued at £20,000/QALY as is usually applied by NICE in the UK for approval of therapies, then the NHS would be prepared to pay £5,500million over 25 years for an intervention that would generate the same number of QALYs.

Table 6. Estimated base case individual and total UK costs and savings over 25 years for an average daily yoghurt intake of 125g. (Means and 95% CI)

	Individual (average) costs		
Costs	Current scenario	Yoghurt scenario	Savings
5 Years	£5,984 (£5,966, £6,002)	£5,981 (£5,963, £5,998)	£3.21 (£2.65, £3.77)
10 Years	£10,883 (£10,854, £10,911)	£10,871 (£10,842, £10,900)	£11.6 (£10.09, £13.1)
15 Years	£15,028 (£14,990, £15,067)	£15,005 (£14,966, £15,043)	£23.65 (£21.08, £26.23)
20 Years	£18,547 (£18,499, £18,595)	£18,509 (£18,461, £18,557)	£37.91 (£34.31, £41.51)
25 Years	£21,493 (£21,436, £21,550)	£21,438 (£21,382, £21,495)	£54.35 (£49.87, £58.82)

	UK population costs		
Costs	Current scenario	Yoghurt scenario	Savings
5 Years	£261,710m (£260,941m, £262,480m)	£261,570m (£260,801m, £262,339m)	£140m (£116m, £165m)
10 Years	£475,955m (£474,697m, £477,214m)	£475,448m (£474,192m, £476,705m)	£507m (£441m, £573m)
15 Years	£657,270m (£655,579m, £658,961m)	£656,235m (£654,549m, £657,922m)	£1,034m (£922m, £1,147m)
20 Years	£811,149m (£809,049m, £813,249m)	£809,491m (£807,397m, £811,584m)	£1,658m (£1,500m, £1,816m)
25 Years	£939,994m (£937,509m, £942,480m)	£937,617m (£935,140m, £940,095m)	£2,377m (£2,181m, £2,573m)



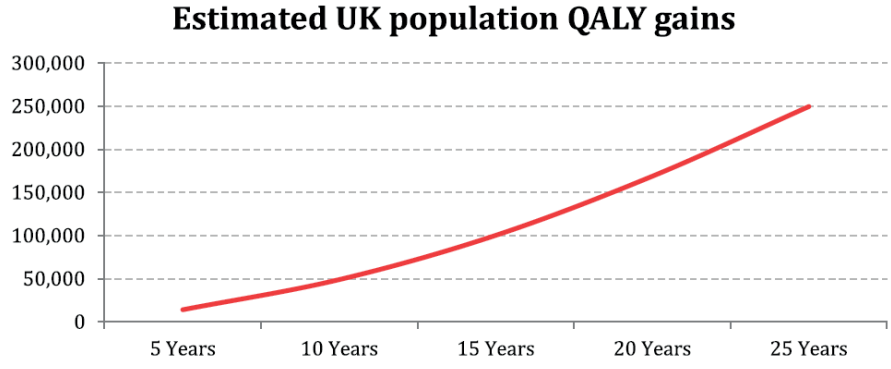
Application of the 0.91 risk reduction of developing T2D from average yoghurt consumption of 125g as opposed to the 0.99 risk reduction from the current average of 20.4g has a relatively modest impact on the absolute annual risk of developing T2D in the model. For people aged 60-69, the annual risk of developing T2D in the model is reduced from 0.67% to 0.62%, which was the largest absolute reduction for any age group. However, whilst the annual absolute risk reduction is modest, over time this reduction results in a substantial number of avoided incident cases of T2D.

In the base case, the model suggests that the absolute reduction in the 25-year risk of developing T2D for a random person over the age of 25 was 0.89% (0.83% to 0.95%). At a

Table 7. Estimated base case individual and total UK QALYs and savings over 25 years for an average daily yoghurt intake of 125g

	Individual (average) QALYs		
QALYs	Current scenario	Yoghurt scenario	Gained QALYs
5 Years	4.3743 (4.3684, 4.3803)	4.3747 (4.3687, 4.3807)	4.3743 (4.3684, 4.3803)
10 Years	8.0515 (8.0372, 8.0657)	8.0528 (8.0386, 8.067)	8.0515 (8.0372, 8.0657)
15 Years	11.1406 (11.1175, 11.1637)	11.1434 (11.1203, 11.1665)	11.1406 (11.1175, 11.1637)
20 Years	13.6927 (13.6608, 13.7245)	13.6973 (13.6654, 13.7291)	13.6927 (13.6608, 13.7245)
25 Years	15.7573 (15.7172, 15.7975)	15.7637 (15.7235, 15.8038)	15.7573 (15.7172, 15.7975)

	UK population QALYs		
QALYs	Current scenario	Yoghurt scenario	Gained QALYs
5 Years	191m (191m, 192m)	191m (191m, 192m)	0.017m (0.015m, 0.020m)
10 Years	352m (352m, 353m)	352m (352m, 353m)	0.060m (0.052m, 0.067m)
15 Years	487m (486m, 488m)	487m (486m, 488m)	0.124m (0.109m, 0.139m)
20 Years	599m (597m, 600m)	599m (598m, 600m)	0.200m (0.177m, 0.223m)
25 Years	689m (687m, 691m)	689m (688m, 691m)	0.276m (0.246m, 0.307m)



population level, this equates to 388,369 (362,939 to 413,800) fewer people developing T2D over 25 years.

From this reduction in the risk of developing T2D there is a consequent reduction in the risk of developing the complications of T2D. This in turn could reduce the NHS burden of treating those complications for each individual as well as increases an individual's quality of life. Specifically, over 25 years the modelling predicts that consumption of an additional daily serving of yoghurt in the whole adult population over 25 years old in the UK would reduce the number of people with:

- A first cerebrovascular event (stroke) by 4,811 (95% CI: 1,968, 7,654);
- Ischemic heart disease by 3,499 (1,074, 5,923);
- Heart failure by 1,749 (35, 3,464);
- A first myocardial infarction by 1,749 (35, 3,464);
- Requiring RRT by 437 (-420, 1,295);
- Diabetic neuropathy by 13,558 (8,786 to 18,330);
- Lower limb amputation by 3,936 (1,365 to 6,508).

The biggest driver of both cost savings and QALY gains in the model results from the reduction in people with T2D itself rather than a reduction in complications. Savings from direct treatment costs of T2D accounts for 91.5% of the total model savings and approximately 85% of the QALY gains.

The model also suggested that increased yoghurt consumption to an average of 125g per day would reduce overall mortality over 25 years by 0.005% (0.001% to 0.009%). This equates to there being 2,187 (95% CI: 270 to 4,104) more people who would still be alive after 25 years if yoghurt consumption increased to an average of 125g.

We undertook sensitivity analyses of the lower and upper confidence interval for the risk reduction of an extra daily serving of yoghurt on T2D risk reported in Chen adjusted for 125g consumption (0.85 to 0.98). This results in a potential saving to the NHS of an increase in average consumption to 125g a day at a population level of between £0.48 billion and £3.80 billion. QALY savings generated varied between 60,940 and 429,831 and deaths averted between 1,749 and 4,374 (tables 4.4 to 4.9).

DISCUSSION

We have demonstrated that if the correlation relationship reported in Chen of increasing yoghurt consumption is causative, then increasing yoghurt consumption could be an effective policy for reducing the incidence of T2D. The patient-level simulation model predicts that if in the UK the average consumption of yoghurt increased from 20.4g to 125g daily (an additional 100g) in people over the age of 25 years old, nearly 400,000 fewer people would develop diabetes over 25 years. Such an approach fits well with National Institute for Health and Clinical Excellence (NICE) 2015 Clinical Guidelines to integrate dietary advice into prevention and T2D, as well as United Nation goals to reduce the impact of non-communicable diseases (NCDs), such as T2D, by reducing modifiable risk factors for NCDs associated with unhealthy diet, physical inactivity and obesity.[25]

In terms of the NHS, an increase in the average consumption of conventional yoghurt could help attenuate NHS expenditure on diabetes already predicted to increase to 17% of the total resources by 2035.[13] Applying the average saving to the UK population over the age of 25 would generate total discounted savings to the NHS of approximately £140 million over five years that would increase to £2.4 billion over 25 years if average consumption increased to 125g.

Additional benefits from increased yoghurt consumption might accrue from direct effects on cardiovascular risks. Evidence that fatty acids in dairy may help improve glucose homeostasis,[9] and daily consumption of probiotic yoghurt has the potential to improve cardiovascular disease risk factors associated with diabetes,[26] provides a rationale for incorporating the consumption of yoghurt into this dietary advice.

Yoghurt consumption can also be recommended in addition to other, more targeted interventions, as the financial cost of purchasing the yoghurt would fall upon the individual rather than the NHS; if the yoghurt was a replacement for other snacks rather than an additional snack, the cost to the individual might be negligible. In a recently published meta-analysis, Gijsbers supports the findings of the Chen study indicating that yoghurt intake may be non-linearly associated with lower risk of T2D, reporting a 14% lower risk for an intake of 80 to 125g per day compared with zero consumption, which appears to be in line with the absolute risk reduction of our base case.[27]

Given the rapidly increasing prevalence of T2D, the findings of this research offer implications for cost-saving measures which may help alleviate the economic burden of diabetes, and relieve pressure on the health care infrastructures in the long term in populations beyond the UK.

Limitations in model

All the analyses related to individuals over the age of 25 and so the model and economic results generated are only for people over the age of 25 years old; however this is reasonable for the condition as T2D is more common after the age of 45.[28]

The Chen meta-analysis[12], on which this research is based, provided longitudinal data from a large number of patients which provides evidence on the RR of developing T2D with different levels of yoghurt consumption, based upon the correlation between the two. The Chen data was also pooled from retrospective food frequency questionnaires capturing participant food intake over the course of a year, so there is likely to be some recall bias in reporting amounts of foods consumed. Chen compiled data from prospective cohort studies, which allows establishment of statistical associations

between events. This does not provide direct proof of effect, individual studies have as much as possible adjusted for confounding factors but the possibility of residual confounding cannot be discarded. To demonstrate causality, randomised controlled intervention trials of increasing yoghurt consumption would be needed. It may be that such studies, including in individuals under 25 years old,[29] should now be planned and undertaken. The Chen meta-analysis did not differentiate between plain, flavoured and sweetened yoghurt. Results from three recent prospective cohorts indicate that weight loss is observed even with sweetened yoghurt consumption, although the benefit is higher for those who eat yoghurt with a low glycemic load.[10] In addition, it has been reported that, when observing consumer sweetening behaviour in contextualised conditions, on average a greater amount of sugar is added in plain yoghurt than that found in commercial pre-sweetened yoghurts.[30] Further research could investigate differences in diabetes incidence rates across the various types of yoghurt.

CONCLUSIONS

Increasing yoghurt consumption in the adult population of the UK by 100g per day could generate substantial cost savings to the NHS as well as significant patient benefit through reductions in the incidence of T2D if the causal relationship between yoghurt consumption and reduced levels of diabetes seen in published studies is confirmed.

REFERENCES

1 World Health Organization. (2014) Global status report on noncommunicable diseases. WHO, Geneva.

2 Mathers CD, Loncar D. (2006) Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 3(11), e442.

3 Shaw JE, Sicree RA, Zimmet PZ. (2010) Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 87(1), 4-14.

4 International Diabetes Federation. (2015) IDF Diabetes atlas: seventh edition. IDF, Brussels.

5 Diabetes Prevention Program Research G. (2012) The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care* 35(4), 723-30.

6 Panahi S, Tremblay A. (2016) The Potential Role of Yogurt in Weight Management and Prevention of Type 2 Diabetes. *J Am Coll Nutr*. 35(8), 717-31.

7 Månsson HL. (2008) Fatty acids in bovine milk fat. *Food Nutr Res*. 52,10. 3402/fnr.v52i0.1821. doi:10.3402/fnr.v52i0.1821

8 Phillips CM, Kesse-Guyot E, McManus R, *et al*. (2012) High dietary saturated fat intake accentuates obesity risk associated with the fat mass and obesity-associated gene in adults. *J Nutr*. 142(5), 824-31.

9 Drehmer M, Pereira MA, Schmidt MI, *et al*. (2015) Associations of dairy intake with glycemia and insulinemia, independent of obesity, in Brazilian adults: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Am J Clin Nutr*. 101(4): 775-82.

10 Smith JD, Hou T, Ludwig DS, Rimm EB, Willett W, Hu FB, Mozaffarian D. (2015) Changes in intake of protein foods, carbohydrate amount and quality, and long-term weight change: results from 3 prospective cohorts. *Am J Clin Nutr.* 101(6), 1216–24.

11 Forouhi NG, Koulman A, Sharp SJ, *et al*. (2014) Differences in the prospective association between individual plasma phospholipid saturated fatty acids and incident type 2 diabetes: the EPIC-InterAct case-cohort study. *Lancet Diabetes Endocrinol.* 2(10), 810-8.

12 Chen M, Sun Q, Giovannucci E, *et al*. (2014) Dairy consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. *BMC Med*. 12, 215.

13 Hex N, Bartlett C, Wright D, Taylor M, Varley D. (2012) Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. *Diabet Med*. 29(7), 855-62.

14 Dalziel K, Segal L. (2007) Time to give nutrition interventions a higher profile: cost-effectiveness of 10 nutrition interventions. *Health Prom Int*. 22(4), 271-83.

15 Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. (2010) Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. *Diabetes Care* 33(8), 1872-94.

16 Age Structure of United Kingdom 1971- 2085. http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/dcp171776_237753.pdf.

17 O'Connor LM, Lentjes MA, Luben RN, Khaw KT, Wareham NJ, Forouhi NG. (2014) Dietary dairy product intake and incident type 2 diabetes: a prospective study using dietary data from a 7-day food diary. *Diabetologia* 57(5), 909-17.

18 Alva ML, Gray A, Mihaylova B, Leal J, Holman RR. (2015) The impact of diabetes-related complications on healthcare costs: new results from the UKPDS (UKPDS 84). *Diabet Med*. 32(4), 459-66.

19 Stevens RJ, Kothari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study G. (2001) The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci (Lond)* 101(6), 671-9.
20 Kothari V, Stevens RJ, Adler AI, *et al*. (2002) UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke* 33(7), 1776-81.
21 Kerr M. (2012) NHS Diabetes: Foot care for people with diabetes: The economic case for change. pp.1-72.
22 Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. (2011) Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making* 31(6), 800-4.
23 Bagust A, Beale S. (2005) Modelling EuroQol health-related utility values for diabetic complications from CODE-2 data. *Health Econ*. 14(3), 217–30.
24 National Diabetes Audit 2011-2012. (2013) Report 2: Complications and mortality. Published by the Health and Social Care Information Centre (HSCIC). http://content.digital.nhs.uk/catalogue/PUB12738/nati-diab-audi-11-12-mortcomp-rep.pdf.
25 WHO. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. (2013) World Health Organization, Geneva.
26 Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V, Akbarian-Moghari A. (2011) Effect of probiotic yogurt containing *Lactobacillus acidophilus* and *Bifidobacterium lactis* on lipid profile in individuals with type 2 diabetes mellitus. *J Dairy Sci.* 94(7), 3288–94.
27 Gijsbers L, Ding EL, Malik VS, de Goede J, Geleijnse JM, Soedamah-Muthu SS. (2016) Consumption of dairy foods and diabetes incidence: a dose-response meta-analysis of observational studies. *Am J Clin Nutr.* 103(4), 1111–24.
28 Hillier TA, Pedula KL. (2001) Characteristics of an adult population with newly diagnosed type 2 diabetes: the relation of obesity and age of onset. *Diabetes Care* 24(9), 1522-7.
29 Amutha A, Mohan V. (2016) Diabetes complications in childhood and adolescent onset type 2 diabetes-a review. *J Diabetes Complicat*. 30, 951–7.
30 Saint-Eve A, Leclercq H, Berthelo S, Saulnier B, Oettgen W, Delarue J. (2016) How much sugar do consumers add to plain yogurts? Insights from a study examining French consumer behavior and self-reported habits. *Appetite* 99, 277–84.
31 Scotland N. (2013) In: Group SDSM, editor. Scottish Diabetes Survey 2013.
32 Townsend WK R, P Bhatnagar, K Smolina, M Nichols, R Luengo-Fernandez. (2012) Coronary heart disease statistics: A compendium of health statistics, 2012 edition.
33 Welsh Health Survey. http://gov.wales/statistics-and-research/welsh-health-survey/?tab=previous&lang=en.
34 Shaw C, Pitcher D, Pruthi R, Fogarty D. (2013) UK Renal Registry 16th annual report: chapter 2 UK RRT prevalence in 2012: national and centre-specific analyses. *Nephron Clin Pract*. 125(1-4), 29-53.
35 Zoccali C, Kramer A, Jager KJ. (2010) Chronic kidney disease and end-stage renal disease—a review produced to contribute to the report 'the status of health in the European union: towards a healthier Europe'. *Clin Kidney J*. 3(3), 213-224. doi:10.1093/ndtplus/sfp127
36 Rothwell PM, Coull AJ, Silver LE, *et al*. (2005) Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories (Oxford Vascular Study). *Lancet* 366(9499), 1773-83.
37 Zhang X, Saaddine JB, Chou CF, *et al*. (2010) Prevalence of diabetic retinopathy in the United States, 2005-2008. *JAMA* 304(6), 649-56.

38 McAlpine RR, Morris AD, Emslie-Smith A, James P, Evans JM. (2005) The annual incidence of diabetic complications in a population of patients with Type 1 and Type 2 diabetes. *Diabet Med.* 22(3), 348-52.

39 Prasad S, Kamath GG, Jones K, Clearkin LG, Phillips RP. (2001) Prevalence of blindness and visual impairment in a population of people with diabetes. *Eye* 15(Pt 5), 640-3.

40 Trautner C, Haastert B, Richter B, Berger M, Giani G. (2003) Incidence of blindness in southern Germany due to glaucoma and degenerative conditions. *Invest Ophthalmol Vis Sci.* 44(3), 1031-4.

41 Abbott CA, Carrington AL, Ashe H, *et al*. (2002) The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med*. 19(5), 377-84.

42 Ahmad N, Thomas GN, Gill P, Chan C, Torella F. (2014) Lower limb amputation in England: prevalence, regional variation and relationship with revascularisation, deprivation and risk factors. A retrospective review of hospital data. *J R Soc Med*. 107(12), 483-9.

43 Johannesson A, Larsson GU, Ramstrand N, Turkiewicz A, Wirehn AB, Atroshi I. (2009) Incidence of lower-limb amputation in the diabetic and nondiabetic general population: a 10-year population-based cohort study of initial unilateral and contralateral amputations and reamputations. *Diabetes Care* 32(2), 275-80.

44 Centre NCG. (2010) Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care. London: National Clinical Guideline Centre.

45 Cowie MR, Wood DA, Coats AJ, *et al*. (2000) Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 83(5), 505-10.

46 Hobbs FD, Roalfe AK, Davis RC, Davies MK, Hare R, Midlands Research Practices C. (2007) Prognosis of all-cause heart failure and borderline left ventricular systolic dysfunction: 5 year mortality follow-up of the Echocardiographic Heart of England Screening Study (ECHOES). *Eur Heart J*. 28(9), 1128-34.

Chapter 9.1

Public health and budget impact of probiotics on common respiratory tract infections: a modelling study

Irene Lenoir-Wijnkoop, Laetitia Gerlier, Jean-Louis Bresson, Claude Le Pen, Gilles Berdeaux

Published in: PLoS One 2015;10(4), e0122765

ABSTRACT

Objectives Two recent meta-analyses by the York Health Economics Consortium (YHEC) and Cochrane demonstrated probiotic efficacy in reducing the duration and number of common respiratory tract infections (CRTI) and associated antibiotic prescriptions. A health-economic analysis was undertaken to estimate the public health and budget consequences of a generalized probiotic consumption in France.

Methods A virtual age- and gender-standardized population was generated using a Markov microsimulation model. CRTI risk factors incorporated into this model were age, active/passive smoking and living in a community setting. Incidence rates and resource utilization were based on the 2011-2012 flu season and retrieved from the French GPs Sentinelles network. Results of both meta-analyses were independently applied to the French population to estimate CRTI events, assuming a generalized probiotic use compared to no probiotics during winter months: -0.77 days/CRTI episode (YHEC scenario) or odds-ratio 0.58 for ≥ 1 CRTI episode (Cochrane scenario) with *vs*. without probiotics. Economic perspectives were National Health System (NHS), society, family. Outcomes included cost savings related to the reduced numbers of CRTI episodes, days of illness, number of antibiotic courses, sick leave days, medical and indirect costs.

Results For France, generalized probiotic use would save 2.4 million CRTI-days, 291,000 antibiotic courses and 581,000 sick leave days, based on YHEC data. Applying the Cochrane data, reductions were 6.6 million CRTI days, 473,000 antibiotic courses and 1.5 million sick days. From the NHS perspective, probiotics' economic impact was about €14.6 million saved according to YHEC and €37.7 million according to Cochrane. Higher savings were observed in children, active smokers and people with more frequent human contacts.

Conclusion Public health and budget impact of probiotics are substantial, whether they reduce CRTI episodes frequency or duration. Noteworthy, the 2011-12 winter CRTI incidence was low and this analysis focused on the fraction of CRTI patients consulting a practitioner.

INTRODUCTION

Common respiratory tract infections (CRTI) include common cold (CC), upper respiratory tract infections, influenza like illness (ILI) and flu.[1-3] CRTI are mainly of viral origin, are contagious and transmitted via airborne droplets, direct contact or through contaminated objects.[4,5] Symptoms include runny nose, sneezing, sore throat, coughing, and sometimes fever, most of the time self-limited and usually resolving in seven to ten days. On average, adults have two to five infections annually and children typically present six to twelve "colds" per year.[1,6] Rates of symptomatic infections increase in the elderly. Overlapping clinical presentations among influenza, CC, upper respiratory tract infections and flu make differential diagnosis difficult.[7,8] Over-the-counter medications can bring relief of symptoms,[9] but do not alter the course of the disease. Antibiotics are recommended only in the case of superinfection.[10]

Although the average cost of a CRTI episode is low, the high incidence and the recurrence rates lead to a high burden for the national health systems (NHS), CC being the most common reason for visiting general practitioners (GP) and for antibiotic prescription in children. In addition, CRTI recurrences affect parents' quality of life.[11] Lastly, non-medical direct costs (e.g. need for babysitting) and absenteeism represent a significant burden.[12,13]

Nutritional intervention trials have investigated the benefits of many different probiotics in the management of CRTI.[14-24] The growing number of studies assessing the impact of probiotics-based interventions reflects the need for a proper measurement of the probiotics effects on given clinical symptoms and/or disease burden. The recent constitution of dedicated interest groups within the Health Technology Assessment international (HTAi) organization and more recently by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) confirms the key role of nutrition, including probiotics, among the possible Public Health strategies.[25,26] Probiotics are easily available for the general population through daily consumption of fermented dairy products or food supplements. At the beginning of this century, the Food and Agriculture Organization (FAO) and World Health Organization (WHO) defined probiotics as "Live microorganisms, which when administered in adequate amounts confer a health benefit on the host".[27] This definition was confirmed recently by an expert consensus group.[28] The likely mechanism of probiotic impact on CRTI is through bolstering immune response; several studies have shown probiotics to increase the numbers of T-lymphocytes and to enhance phagocytosis, natural killer cell activity, and IgA production.[29] Probiotic health effects are often regarded as strain-specific. However the results of many meta-analyses, including the two studies applied in this paper, pool data on similar clinical

outcomes achieved by different *Lactobacillus* and *Bifidobacterium* species and strains. This supports the concept that some effects may be common among a range of strains. Recently, experts supported this concept for several public health benefits associated with a cross section of probiotics.[30] Three meta-analyses were conducted in the area of CRTI. The first one, from the Cochrane Library, stated that ". . . probiotics were better than placebo when measuring the number of participants experiencing episodes of acute upper respiratory tract infection".[31] Comparable results were reported by the York Health Economics Consortium (YHEC) who conducted a systematic review followed by a meta-analysis. They found that individuals who received probiotics had significantly shorter episodes of CRTI by almost one day compared to those receiving a placebo.[32] The third one focused on the prevention of common colds and excluded other upper respiratory tract diseases. It showed a protective effect of probiotics of borderline significance.[33]

We hypothesize that reducing the duration or the incidence of CRTI during the winter season will influence health care utilization and associated expenditures in Western Europe countries.

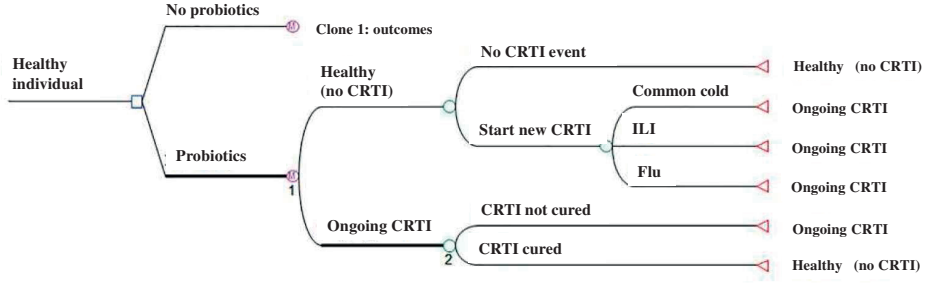
OBJECTIVES

The purpose of our study was to estimate the public health impact and related budget consequences of probiotics use, pertaining to a reduction of the duration (YHEC scenario) or the incidence (Cochrane scenario) of CRTI, applied to France as a representative Western Europe country.

METHODS

This analysis was conducted according to the French recommendation on methods for health economics evaluation published by the Haute Autorité de la Santé, which advises the use of models to estimate the Public Health and economic effects of new health care intervention.[34] No Ethics Committee submission nor informed consents were required for our study since it did not involve any patient recruitment nor individual records consultation. All inputs were retrieved from publicly available sources as described in the next sections.

Figure 1. Markov model structure 'probiotics *vs*. no probiotics' (TreeAge software display)



M nodes: indicates Markov nodes (starting point of simulation). Circles: indicates a chance node (probability needed). Triangle: indicates a terminal node, Square: decision node. ILI: influenza-like illness. The model compares a strategy without probiotics to a strategy with probiotics intake. All individuals were supposed healthy at model entry. Over the model course, the possible outcomes, with strategy-specific probabilities, are to develop a new CRTI or to remain healthy. In case of a new CRTI event, the cases are split into common cold, non-flu ILI, and flu. In case of ongoing CRTI, the possible outcomes are to be cured or to remain sick with CRTI.

Model description

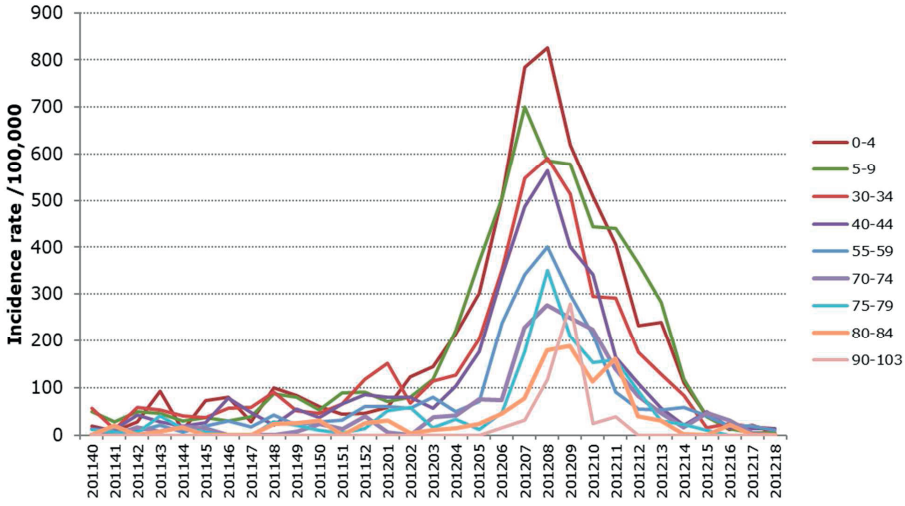
A state-transition microsimulation (individual-based) Markov model was developed using TreeAge Pro 2009. Two health states were considered: "Healthy" and "CRTI" (Fig 1). The Markov cycle length (the time periodicity of updating all model parameters) was 1 day and time horizon was 217 days, covering a winter season from October until April to match the usual monitoring activity of the flu cases in European networks, including the French 'Sentinelles'.[35]

A virtual population approach based on first-order Monte-Carlo simulations was used, as recommended by Gueyffier *et al*.[36] Healthy individuals entered the model at the beginning of the season of "winter colds". A sampling rate of 1/1000 represented the French population structure (by gender and 5-year age ranges to reproduce the Sentinelles data) and Sentinelles' ILI incidence rates per age (Figure 2). This model included neither herd immunization (probiotic effect was limited to the consumer) nor self-immunization. Therefore, cured subjects joined back the general population and its exposure to CRTI.

Study population and comparator

The population was representative of the French population, according to demographics and known risk factors of developing CRTI (age, passive or active smoking, living in a community setting). The evaluated strategy was a generalized (100%) use of probiotics among the French population aged 3 to 79 years-old while the reference strategy was placebo *i.e*. the absence of probiotics use. The maximal probiotic effect was therefore estimated, in the absence of published data on the current probiotic consumption.

Figure 2. Weekly influenza-like illness incidence rate (/100,000) according to Sentinelles network by age for the epidemic period of winter 2011–2012



yo: year-old. Source: réseau Sentinelles, INSERM/UPMC, http://www.sentiweb.fr Accessed 24 March 2015. Age is a risk factor for CRTI. The figure shows that the ILI incidence during the epidemic season (weeks 5 to 12 of 2012, during winter 2011–2012) is age-dependent. Children aged between 0 and 9 years have the highest incidence rates, up to 434 cases/100,000 at season's peak.

Epidemiological sources

The size of the French population per age group and gender in 2012 was obtained from Eurostat.[37] In 2012, the French metropolitan population was 65.4 million, of which 59.3 million aged between 3 and 79.

The Sentinelles GP network records ILI in the general French population to identify flu outbreak at a national level. ILI is defined as sudden fever higher than 39°C (102°F), myalgia and respiratory signs. It includes 'real flu' and 'non flu' ILI cases. For our broader CRTI modelling purpose, 'non flu' ILI and flu cases were split, and then CC occurrence was extrapolated using a large observational study which reported relative ratio of CC/flu over several winter seasons.[38]

CRTI probabilities in the general population

Three types of CRTI were considered in the model: CC, ILI and flu. The daily probability to develop a CRTI was derived from the weekly number of ILI cases reported by Sentinelles. The probability was adjusted for environmental known risk factors: age, passive or active smoking, living in a community setting.

CRTI risk factor: age

Children and elderly were more prone to visit their doctor for ILI, as shown in Figure 2. According to Fleming and Ayres, the number of CC episodes per 1 ILI was higher in the younger age groups: 3.04 in the 0–4 year old population, 1.73 in the 5–14, 1.05 in the 15–44, 1.09 in the 45–64 and 1.92 among those aged 65 or above.[34]

CRTI risk factor: smoking status

Benseñor *et al*. found a significant increase in the average duration of a CC episode in active smokers (Relative Risk [RR] of duration >7 days = 1.62 [1.40;1.87] in light smokers, 2.63 [2.02;3.44] in smokers of ≥ 25 cigarettes per day).[39] CRTI duration was assumed to be +16.8% in active smokers. In passive smokers, a significantly longer duration of CRTI (adjusted RR of having a cold lasting over 7 days = 1.12 [0.99;1.27] *vs*. never smokers) and a significantly higher incidence of colds (adjusted RR of having at least one cold = 1.15 [1.05;1.26] *vs*. never smokers) were reported. CRTI duration was assumed to be +4.5% in passive smokers *vs*. non-smokers. Prevalence of active smoking by age and gender was obtained from the French National Institute for Statistics and Economic Studies (INSEE) in 2010.[40] The probability to be a passive smoker among the non-smoking population was fixed as equal to the proportion of active smokers in the general population (Table 1).

CRTI risk factor: living in a community setting

Children between 1 and 7 years old attending day care centers had significantly more CC (RR = 1.22 [1.13;1.31]) compared to children in private home care.[41] Adults working in shared office had an increased risk of developing CC compared to those working in individual offices (adjusted OR for having 2 or more CC = 1.35 [1;1.82]).[42] The OR for having at least one CC in the past 12 months was 1.64 [1.08;2.49]. The rates of school and university attendance and of adults working in a shared office were retrieved from INSEE.[40]

Effect of probiotics on CRTI

Two simulations were conducted independently, using the results from the two meta-analyses. Both analyses are thus based on different assumptions.

YHEC scenario. In a first scenario, the results from the YHEC meta-analysis were used. Based on 9 studies (see main characteristics in Table 2), including a total of 1577 probiotics-receiving *vs*. 1774 placebo-receiving individuals, the mean duration of CRTI illness was 0.77 days [-1.50;-0.04] shorter in the probiotic arm (p = 0.04). The average duration of a CRTI episode was 7 days in the placebo group, which was the duration used in our "no probiotics" control arm.[32]

Table 1. Summary of model inputs – Epidemiological parameters

Model parameters	**Value**	**Sampling information**	**Reference**
Season start-end	Oct 2011-Apr 2012		Sentinelles definition
Time horizon (days)	217		Season duration
French population size 3-79 yo	59,316,541	Rate 1/1000	Eurostat 2012
Risk factors	**% population**	**Sampling information**	**Reference**
***Age (years)**		uniform, /sex, age group	
3 to 9	9.6%		Eurostat 2012
10 to 24	20.3%		
25 to 64	57.3%		
65 to 79	12.8%		
***Active smoker**	24.5%	uniform, /sex, age group	OFDT 2010
***Passive smoker**	18.5%	uniform, /sex, age group	Assumption
***Living in a community setting**		uniform, /sex, age group	
Attending school (3-9)	99.5%		DEPP 2010-11
Students (10-24)	79.1%		DEPP 2010-11
Employed, in open-space (25-64)	35.8%		INSEE 2011
Living in an institution (65-79)	2.8%		EHPA 2003
RTI characteristics	**Incidence/100,000**	**Duration (days)**	**Reference**
CC	2,429	7	Fleming & Ayres 1988 (N CCs:ILI)
ILI	1,758	7	Sentinelles CRTIs - flu cases
Influenza	1,548	7	Fleming & Ayres 1988 (N flu: ILI+flu)
Total CRTI incidence	5,735	7	Sentinelles 2011-12 + Fleming & Ayres 1988
Impact of risk factors:	***on CRTI incidence***	***on CRTI duration***	**Reference**
***Age (years)**	*per 100,000*	*N days*	
3 to 9	13,347	7	Sentinelles 2011-12; YHEC 2012
10 to 24	5,960	7	Sentinelles 2011-12; YHEC 2012
25 to 64	4,975	7	Sentinelles 2011-12; YHEC 2012
65 to 79	3,098	7	Sentinelles 2011-12; YHEC 2012
***Active smoker**	NA	+4.5% *vs*. no smokers	Benseñor 2001
***Passive smoker**	RR=1.15 *vs*. no smokers	+16.8% *vs*. no smokers	Benseñor 2001
***Living in a community setting**			
Day care (e.g. school) *vs.* home care	RR=1.22	NA	Louhiala 1995
Shared office *vs*. alone	RR=1.07*	NA	Jaakkola 1995

Table 1. Summary of model inputs – Epidemiological parameters (*continued*)

Model parameters	Value	Sampling information	Reference
Impact of using probiotics:	***on CRTI incidence***	***on CRTI duration***	***on AB use***
Reference YHEC 2012	NA	-0.77 days *vs*. pbo	NA
Reference Hao 2011	RR=0.72 *vs*. pbo**	NA	RR=0.67 *vs*. pbo

EHPA: Elderly hosting institutions; DEPP: Directorate for assessment and forecasting and performance; INSEE: National Institute of Statistics and Economic Studies; OFDT: French Monitoring Centre for Drugs and Drug Addiction; SPILF: Society of Infectious Pathology of French language; yo: year-old

*OR = 1.64;

**OR = 0.58.

Conversions into RR using exact numbers of events and sample sizes.

COCHRANE scenario. In a second scenario, results from the Cochrane meta-analysis were considered. The odds ratio for having at least 1 CRTI episode was 0.58 [0.36;0.92] (p = 0.022), based on 6 studies (Table 2) including a total of 940 individuals in the probiotics arm *vs*. 896 in the control arm. This ratio was converted into a relative risk of 0.72, and applied to the baseline CRTI risk to obtain the probability of having a CRTI in the probiotics arm of the model.[31] Note that only the likelihood of decreased symptoms was reported, and not the likelihood for the CRTI infection to be transmitted (static model).

In both meta-analyses, the included studies lasted generally for 3 months, including the winter months. The probiotic dosage was between 10^8 and 10^{10} colony forming units (CFU) per day, via oral consumption.

Resources utilization

The resources utilization included in the model were GP visits, antibiotics, non-antibiotic drugs prescribed and sick leave days. Mosnier *et al*. reported an ILI antibiotic prescription rate of 15% in children aged 1–12 and 34.1% in adults.[43] According to Hao, patients consuming probiotics had lower antibiotic prescription *vs*. controls (risk ratio of 0.67 [0.45;0.98] (p = 0.04)).[31] Cohen *et al*. reported the number of visits and drug prescription costs in ILI patients, according to disease severity.[44] The authors defined "Mild" as the need for 1 GP consultation, no sick leave and no complication (56%), "Moderate" included a single GP visit at the patient's home and/or a sick leave (28%), and "Severe" cases were complicated cases requiring more than 1 GP visit (16%). A weighted average cost was calculated based on the relative frequency of severity.

EcoGrippe reported that 70% of employed individuals consulting for CRTI received a sick leave prescription for an average duration of 4.8 days, and 25% of employees took a sick leave because of sick children for an average duration of 3.0 days.[13] Table 3 describes the resource use parameters included in the model and their sources.

Table 2. Main characteristics of the studies included in the YHEC and Cochrane meta-analyses

Reference YHEC	Country	Population	Duration	Total probiotic dose per day	Comparator
Bentley 2008 (unpublished)	Germany	Adults at increased risk of infection (at least 2 episodes in the previous 6 months)	12 weeks	$1x10^9$ CFU	Placebo: sachet containing maltodextrin without living cultures.
Berggren, Lazou Ahren *et al*. 2011	Sweden	Healthy adults aged 18–65 years.	12 weeks	$1x10^9$ CFU	Placebo: 1.0g maltodextrin powder sachet.
Cáceres *et al*. 2010	Chile	Children (1 to 5 years of age) attending day care centres.	3 months	$1x10^8$ CFU	Placebo: milk product with no probiotic.
de Vrese. 2005	Germany	Healthy adults (aged 18–67).	3 months then 5.5 months	$5x10^7$ CFU	Placebo: vitamin mineral preparation without probiotic.
Guillemard *et al*. 2010	Germany	Adults aged 18–65 years; working in 2- or 3-shift work patterns (including night work).	3 months	1.1×10^9 CFU	Placebo: a non-fermented, acidified, sweetened, flavoured dairy drink without the active components.
Guillemard *et al*. 2010	France	Male and female individuals of at least 70 years of age who were free-living (not residing in an institution).	3 months	1.1×10^9 CFU	Placebo: a non-fermented, acidified, sweetened, flavoured dairy drink without the active components.
Kloster Smerud 2008	Norway	Children (12-36 months) attending day care centres.	7 months	1.5×10^{10} CFU	Placebo: ordinary fermented milk drink heated to 75 degrees Celsius for 4 seconds to ensure absence of probiotic bacteria (raspberry flavoured).
Niborski *et al*. (unpublished)	France	Healthy adults (mostly men).	7 weeks	NA	Placebo: acidified milk (no bacteria).
Turchet *et al*. 2003	Italy	Free-living elderly people over 60 years of age.	3 weeks	$1x10^9$ CFU	No study product.
Reference Cochrane	**Country**	**Population**	**Duration**	**Total probiotics dose per day**	**Comparator**
Berggren 2010	Sweden	Health volunteers aged 18 to 65	12 weeks	1× 9 10~9 CFU	Placebo
Hojsak 2010a	Croatia	Children aged 13 to 86 months attending daycare centre.	4 months	10~9 CFU	Same post-pasteurised fermented milk product

Table 2. Main characteristics of the studies included in the YHEC and Cochrane meta-analyses (*continued*)

Reference Cochrane	Country	Population	Duration	Total probiotic dose per day	Comparator
Hojsak 2010b	Croatia	all patients older than 12 months and hospitalised at the paediatric department	Hospitalisation duration (average 5 days)	10~9 CFU	Same post-pasteurised fermented milk product
Kekkonen 2007	Finland	those who participated in the Helsinki city marathon.	3 months	4×10^{10} bacteria (bottle) Or 1.0×10^{10} CFU (capsules)	Placebo
Rautava 2009	Finland	0 to 2 months infants	12 months	1×10^{10} CFU	Placebo
Sanz 2006	Spain	All children aged 3 to 12 studying in selected schools	20 weeks	NA	Placebo

CFU: colony-forming units

Economic perspective

Three economic perspectives were considered: the NHS (direct medical costs paid by the public insurer), the society (NHS + indirect costs due to productivity losses) and the family (medical co-payments and revenue losses in case of sick leave). The unit costs of medications and medical visits were retrieved from the French NHS website.[45] Medical costs were updated for 2012, using the evolution of the harmonized consumer price index for pharmaceuticals between 2001 (96.14) and 2012 (101.81).[40] An allowance of 31.37€/day was applied for sick leave according to the NHS perspective (French Court of Auditors report).[46] The French NHS does not provide daily allowance for the first 3 days of sick leave, the loss from the family perspective was estimated at 109.55€/day (annual net income in France in 2011 was 23,882€ per person, for an average of 218 working days).[40] From the society perspective, the value of a working day loss was estimated at 142.5€, obtained by dividing the gross domestic product (GDP) per capita by the average number of working days per year.[40]

The cost of the probiotics from the family perspective was addressed separately and estimated using the average probiotic dosages and durations of the studies as presented by the YHEC and Cochrane meta-analyses (Table 1), combined with the cost price of probiotic products, derived from national supermarkets. Based on this, a range of cost for a 4-person family was estimated.

Table 3. Summary of model inputs—Resource utilization parameters

Population age ranges	**3-14 yo**	**15-64 yo**	**65-79 yo**	**Reference**
GP visits (common cold; ILI/flu)	1.1;1.4	1.0;1.2	1.0;1.3	Cohen 2001
% with antibiotics course	15.0%	34.1%	34.1%	Mosnier 2002
N distinct medications prescribed	3.7	3.7	3.7	SPILF 2005
Unit costs (€)	**Society**	**NHS**	**Family**	**Reference**
GP visit	31.2	15.1	16.1	ameli.fr 2013
Antibiotic course	5.2	2.9	2.3	BdM_IT 2013
Non-antibiotic drugs (range)	2.6-7.4	1.2-4.3	1.4-3.1	Cohen 2001
Total cost per CRTI episode (€)	**Society**	**NHS**	**Family**	**Reference**
3-14 year-old (common cold;ILI/flu)	46.7;55.6	22.4;27.0	24.3;28.7	Resource use x unit cost
15-64 year-old (common cold;ILI/flu)	45.5;52.0	22.3;25.6	23.1;26.4	Resource use x unit cost
65-79 year-old (common cold;ILI/flu)	61.4;61.9	32.7;31.8	28.7;30.1	Resource use x unit cost
Total population (common cold;ILI/flu)	47.7;53.9	23.7;26.6	24.0;27.2	Resource use x unit cost
Indirect cost parameters	**15-24 yo**	**25-49 yo**	**50-64 yo**	**Reference**
% employed adults	29.9%	81.6%	54.8%	INSEE 2011
Sick leave prescriptions:	**%**	**Mean duration (days)**	**Assumption**	**Reference**
for sick children (aged 3-14)	25.0%	3.0	Assuming parents aged 25-49 year-old	Cohen 2007
for employed adults (aged 15-64)	70.0%	4.8	See employment rates above	Cohen 2007
Unit cost of a working day lost (€)	**Society**	**NHS**	**Family**	**Reference**
Day loss, up to 3 days	142.5	0.0	109.6	GDP/capita, avg net income 2012
Day loss, as from Day 4	142.5	31.4	0.0	Avg daily allowance 2012

The public health outcomes of our model show the number of CRTI episodes (separately for CC, ILI and flu), number of CRTI-days, number of antibiotic courses, number of sick leave days. The economic outcomes included the direct medical costs (medical honoraria, antibiotics and prescribed non-antibiotics drugs) and indirect costs (productivity loss). All outcomes were estimated for the French general population likely to consume probiotics (3–79 years of age, N = 59,300,000) and are presented separately depending on the related scenario (YHEC or Cochrane).

RESULTS

Anchoring of the model was demonstrated; the demographics and Sentinelles data were reproduced with an error rate inferior to 5%. The first scenario analysis (YHEC) showed that the reduced duration of CRTI by almost 1 day due to probiotics led to 2.383 million fewer days with CRTI, while 291,000 antibiotics courses were avoided and the number of prescribed sick leave days diminished by 581,000 days in the arm using probiotics compared to no probiotic consumption. In the second scenario (Cochrane), the reduction of incidence of CRTI episodes with probiotics *vs*. without probiotics showed a higher overall impact on public health than a reduction of duration. Extrapolated to the French situation, the results represented a reduction of 6.639 million CRTI days, the number of antibiotic prescriptions was reduced by 473,000 and 1,453,000 prescribed sick leave days were avoided during the 2011–2012 winter season. (Table 4).

Table 4. Public Health impact of probiotics (model population 3–79 year-old, N = 59,300)

YHEC meta-analysis	**Probiotics**	**No probiotics**	**Difference**
N episodes CC	1,277	1,277	0
N episodes ILI	941	941	0
N episodes flu	880	880	0
N CRTI episodes (any)	**3,098**	**3,098**	**0**
N days CC	8,248	9,230	-982
N days ILI	6,098	6,822	-724
N days flu	5,730	6,407	-678
N CRTI days (any)	**20,076**	**22,459**	**-2,383**
N courses antibiotics	590	881	-291
N sick days	4,278	4,860	-581
Cochrane meta-analysis	**Probiotics**	**No probiotics**	**Difference**
N episodes CC	929	1,291	-362
N episodes ILI	683	986	-303
N episodes flu	585	838	-253
N CRTI episodes (any)	**2,197**	**3,115**	**-918**
N days CC	6,695	9,303	-2,607
N days ILI	4,964	7,151	-2,187
N days flu	4,260	6,105	-1,846
N CRTI days (any)	**15,919**	**22,559**	**-6,639**
N courses antibiotics	426	899	-473
N sick days	3,509	4,962	-1,453

To extrapolate to the France level, a factor x1000 can be applied to the above figures.
CC: common cold; CRTI: common respiratory tract infection; ILI: influenza-like illness

Savings associated with the effect of probiotic use as reported by the YHEC study were estimated at €84.4 million, €14.6 million and €16.2 million, for the society, the NHS and the family, respectively. Using the Cochrane meta-analysis results, these figures amounted to €253.6 million, €37.7 million and €131.1 million, respectively (Table 5). For the society and the family perspectives, savings were mainly generated by fewer days of sick leave.

Table 5. Probiotic savings according to the perspective and the meta-analyses (€ 2012), population aged 3–79 (N = 59.3 million)

Society - YHEC	**Probiotics**	**No probiotics**	**Difference**
Cost visits	148,331	148,331	0
Cost antibiotics	3,093	4,617	-1,524
Cost sick days	609,541	692,372	-82,831
Total cost	**760,965**	**845,320**	**-84,355**
NHS - YHEC			
Cost visits	72,356	72,356	0
Cost antibiotics	1,718	2,564	-846
Cost sick days	35,454	49,255	-13,801
Total cost	**109,528**	**124,175**	**-14,647**
Family - YHEC			
Cost visits	75,962	75,962	0
Cost antibiotics	1,381	2,062	-681
Cost sick days	344,720	360,194	-15,474
Total cost	**422,063**	**438,218**	**-16,155**
Society – Cochrane			
Cost visits	104,968	149,110	-44,142
Cost antibiotics	2,231	4,708	-2,477
Cost sick days	499,969	706,947	-206,978
Total cost	**607,168**	**860,765**	**-253,597**
NHS – Cochrane			
Cost visits	51,247	72,800	-21,553
Cost antibiotics	1,239	2,615	-1,376
Cost sick days	36,128	50,934	-14,806
Total cost	**88,614**	**126,349**	**-37,735**
Family – Cochrane			
Cost visits	53,711	76,296	-22,585
Cost antibiotics	996	2,103	-1,107
Cost sick days	258,143	365,534	-107,391
Total cost	**312,850**	**443,933**	**-131,083**

YHEC: York health economic consortium. Estimated range of average cost of probiotics: 126€ to 336€, for a 4-member family, assuming a daily consumption of one serving of 100mg during a period of 7 months.

Assuming a daily consumption of one serving (100mg) of probiotics, during a period of 7 months, the average cost of probiotic consumption through currently available products was ranging from 126€ to 336€ for a 4-member family. From the NHS perspective, savings were mainly generated by fewer visits and non-antibiotic drugs, followed by fewer antibiotic prescriptions, as the cost of probiotics does not incur to the NHS.

Table 6 reports the above results according to sub-populations exposed to environmental risk factors. From a society perspective and based on the YHEC study, children aged 3–9 would benefit most from probiotics. They represent 9.6% of the population, but 20.4% of the total CRTI days saved and 14.3% of the potential health-economic savings generated by probiotics. They are followed by subjects living or working in a community setting who represent 45.3% of the population, but 52.6% of the CRTI days saved and 48.9% of the savings. Passive smokers also generated higher savings than the general population, followed by active smokers. Cochrane-based results were similar: the consumption of probiotics has a larger impact in people living/working in a community setting followed by children of 3–9 years old.

Table 6. Analysis by risk factors (age, smoking, living in the community), population aged 3–79, society perspective

	Probiotics	**No probiotics**	**Difference (% of total)**
YHEC – Age 3-9 (9.6%)			
Total CRTI days	3,973	4,458	-485 (20.4%)
Cost honoraria	30,870	30,870	0
Cost AB	332	495	-163 (10.7%)
Cost sick days	43,085	54,950	-11,865 (14.3%)
Total cost	**74,286**	**86,315**	**-12,029 (14.3%)**
YHEC – Passive smoker (18.3%)			
Total CRTI days	4,370	4,888	-517 (21.7%)
Cost honoraria	32,423	32,423	0
Cost AB	631	941	-311 (20.4%)
Cost sick days	117,681	134,288	-16,608 (20.0%)
Total cost	**150,734**	**167,652**	**-16,918 (20.1%)**
YHEC – Active smoker (24.5%)			
Total CRTI days	4,867	5,393	-527 (22.1%)
Cost honoraria	31,732	31,732	0
Cost AB	820	1,224	-404 (26.5%)
Cost sick days	188,885	211,776	-22,891 (27.6%)
Total cost	**221,437**	**244,732**	-23,295 (27.6%)
YHEC – Community (45.3%)			
Total CRTI days	10,482	11,734	-1,253 (52.6%)

Table 6. Analysis by risk factors (age, smoking, living in the community), population aged 3–79, society perspective (*continued*)

	Probiotics	No probiotics	Difference (% of total)
Cost honoraria	77,838	77,838	0
Cost AB	1,338	1,997	-659 (43.3%)
Cost sick days	248,063	288,645	-40,583 (49%)
Total cost	**327,239**	**368,481**	**-41,242 (48.9%)**
Cochrane – Age 3-9 (9.6%)			
Total CRTI days	2,898	4,097	-1,199 (18.1%)
Cost honoraria	20,075	28,417	-8,342 (18.9%)
Cost AB	216	457	-240 (9.7%)
Cost sick days	35,848	50,676	-14,828 (7.2%)
Total cost	**56,140**	**79,550**	**-23,410 (9.2%)**
Cochrane Passive smoker (18.3%)			
Total CRTI days	3,301	4,725	-1,424 (21.4%)
Cost honoraria	21,857	31,270	-9,413 (21.3%)
Cost AB	436	941	-505 (20.4%)
Cost sick days	96,022	140,385	-44,363 (21.4%)
Total cost	**118,315**	**172,596**	**-54,281 (21.4%)**
Cochrane Active smoker (24.5%)			
Total CRTI days	3,894	5,420	-1,526 (23%)
Cost honoraria	22,960	32,083	-9,123 (20.7%)
Cost AB	591	1,231	-640 (25.8%)
Cost sick days	150,517	211,592	-61,076 (29.5%)
Total cost	**174,068**	**244,907**	**-70,839 (27.9%)**
Cochrane – Community (45.3%)			
Total CRTI days	8,490	12,075	-3,585 (54%)
Cost honoraria	56,050	79,888	-23,838 (54%)
Cost AB	1,015	2,145	-1,130 (45.6%)
Cost sick days	226,803	319,391	-92,588 (44.7%)
Total cost	**283,868**	**401,423**	**-117,555 (46.4%)**

To extrapolate to the France level, a factor x1000 can be applied to the above figures.

DISCUSSION

A model was developed to extrapolate the results of two meta-analyses investigating the effect of probiotics (over placebo) on CRTI as compared to no probiotic consumption. The model was able to correctly reproduce the current incidence pattern of CRTI during a winter season, in France. The effect of using probiotics on CRTI duration or incidence as per the meta-analyses was then simulated. The estimated public health impact was

significant for France, a country of 65 million inhabitants: up to 6.6 million fewer days with CRTI, 473.000 avoided prescriptions of antibiotics and 1.45 million sick leave days could be saved. The budget saving is commensurable: up to €254 million for the society, €131 million for the family and €37.7 million for the French NHS.

It is important to interpret these results in a population-based framework, as the average benefit shown in the meta-analyses (e.g. 0.77 CRTI days averted) might seem minor at the individual level, while the effect applied to a broad population becomes significant. Importantly, the analysis was conducted on the CRTI patients consulting their general practitioner. In France this represents 37% of the population suffering from from flu symptoms with fever and only 1% of those with common colds symptoms.[47,48] Our analysis thus ignored non-prescribed absenteeism and presenteeism. This leads to an important underestimation of productivity losses related to CC, reported as high by several authors.[12,49]

In addition, the winter season studied (2011–2012) was associated with a low incidence rate of ILI (3,258 per 100,000 while rates since 2008–09 ranged from 4,385 to 6,344 per 100,000). The impact of probiotic consumption would be expected to be greater in seasons with higher incidence rate of CRTIs. On the other hand, we remind that the modelization measured the maximum effect of using probiotics in the 3–79 years old population compared to no probiotic consumption. In reality, a proportion of the French population currently consumes probiotic products and will already experience the associated benefits, while generalized consumption is unlikely to be achieved. No reliable data on the actual consumption of probiotics in French families could be obtained, especially when it comes to differentiate occasional from regular users. This model however is designed to receive further data input on the actual consumption if this becomes available. A hypothetical value of one third (33%) of probiotics users in the general population aged 3–79 was tested. In this simulation, the number of averted CRTI days decreased from 2,4 million (base case YHEC scenario) to 1,6 million and the number of averted CRTI episodes decreased from 0.9 million (base case Cochrane scenario) to 0.6 million. Reduction of health care expenditures will decrease proportionally, but potential cost-savings remain of interest.

Another limitation of our analysis concerns the cost of the evaluated intervention (probiotics) that could not be precisely estimated given the range of available probiotic products. From the household and society perspectives the extra cost was estimated around €230 (€126–336) for the CRTI season for an average family with 2 children, but could be lower if the probiotic replaces other traditional dairy products that are already part of the French traditional eating habits. Compared to a classic pharmaco-economic

analysis, in which the drug cost is generally set at the national or even European level, the cost of a food purchase does normally not weigh on the NHS expenses. In this regard, the impact of nutrition-associated health strategies on the NHS budget is comparable to the one of influenza vaccination policy: young healthy individuals not targeted by the national recommendations can decide to purchase the vaccine to avoid the flu, which leads to savings with no or limited extra expenses for the NHS. Simulations tools were successfully used in Europe to demonstrate the benefits of protecting/vaccinating healthy individuals against influenza from the NHS perspective.[50,51] Such tools may therefore be of interest in nutrition-oriented public health strategies as well.

Contrary to the above-mentioned tools, we did not include the indirect protection of individuals (called "herd immunity", *i.e.* reduced disease's opportunities to be passed on) arising from the averted CRTI cases/days in those using probiotics: modelling a dynamic transmission of CRTI would indeed require a lot more inputs and assumptions, especially on pathogens' infectiousness, immunity duration and between-individuals contact patterns. We focused on two determinist scenarios, and therefore sensitivity analyses are not reported in the results section. We estimated afterwards that the most impactful scenario (Cochrane) might avert between 500,000 and 1,000,000 CRTI cases per season, given the low and high values of the relative risk (RR = 0.65 to 0.81). It should also be noted that the inclusion of risk factors was assumed independent from each other. Most probably, the effect of having concomitant risk factors on the CRTI risk is less than the multiplication of the relative risks.

Further limitations include the extrapolation of the results to other countries and seasons: the model was applied to France. In terms of public health impact it is likely that a pro rata to the population size of other countries might give a rough estimate, especially for the neighboring countries because of free cross-border circulation in the European Union. Similar ILI incidence databases are however necessary for properly adapting the model inputs to another country. As said above, the 2011–2012 season used in the analysis was characterized by a low ILI incidence compared to average rate over the last five winter ILI epidemics. Finally, we limited the effect of probiotics to environmental risk factors to mimic a consumer behavioral approach.

CONCLUSION

The effect of probiotics on CRTI, as supported by two-meta-analyses and extrapolated with our model, is significant on public health and budget in a country like France and shows positive consequences to all economic agents. It benefits the NHS, the society, and

the family. Children and people living in a community setting have higher incremental benefits, because of their higher exposure to respiratory viruses, in combination with an immune system that is either "under construction" (children) or "declining" (elderly).[52,53] Prevention is an important aspect of health. Hand washing and face masks have already showed some effectiveness in the control of spreading CRTI.[54] Probiotics could also be taken into consideration when searching for population-oriented strategies for limiting CRTI in primary health care and household settings during the winter season.

REFERENCES

1 Eccles R. (2005) Understanding the symptoms of the common cold and influenza. *The Lancet Infectious Diseases* 5, 718–725.

2 Boivin G, Hardy I, Tellier G, Maziade J. (2000) Predicting influenza infections during epidemics with use of a clinical case definition. *Clin Infect Dis* 3, 1166–1169.

3 Navarro-Mari JM, Perez-Ruiz M, Cantudo-Munoz P, Petit-Gancedo C, Jimenez-Valera M, Rosa-Fraile M. (2005) Influenza-like illness criteria were poorly related to laboratory-confirmed influenza in a sentinel surveillance study. *Journal of clinical epidemiology* 58, 275–279.

4 Mäkelä MJ, Puhakka T, Ruuskanen O, Leinonen M, Saikku P, Kimpimäki M, *et al*. (1998) Viruses and bacteria in the etiology of the CC. *J Clin Microbiol*. 36, 539–542.

5 Arroll B. Common cold. (2011) *Am Fam Physician* 84, 1390–1391.

6 Simasek M, Blandino DA. (2007) Treatment of the common cold. *American Family Physician* 75, 515–20.

7 Van Cauwenberge P, Berdeaux G, Morineau A, Smadja C, Allaire JM. (1999) Use of diagnostic clusters to assess the economic consequences of rhinopharyngitis in children in Italy and France during the winter. Rhinitis Survey Group. *Clin Ther*. 21, 404–421.

8 Heikkinen T, Järvinen A. (2003) The common cold. *Lancet* 361, 51–59.

9 Kim SY, Chang YJ, Cho HM, Hwang YW, Moon YS. (2009) Non-steroidal anti-inflammatory drugs for the common cold. *Cochrane Database Syst Rev* 3, CD006362. doi:10.1002/14651858.CD006362.pub2

10 Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. (2013) *Cochrane Database Syst Rev* 6:CD000247. doi:10.1002/14651858.CD000247.

11 Berdeaux G, Hervié C, Smajda C, Marquis P. (1998) Parental quality of life and recurrent ENT infections in their children: development of a questionnaire. Rhinitis Survey Group. *Qual Life Res*. 6, 501–12.

12 Nichol KL, D'Heilly S, Ehlinger E. (2005) Colds and influenza-like illnesses in university students: impact on health, academic and work performance, and health care use. *Clin Infect Dis*. 40, 1263–1270.

13 Cohen JM, Mosnier A, Daviaud I, Grog I. (2007) Ecogrippe: combien coûte la grippe? XIIème Journée Nationale des GROG—Paris.

14 Berggren A, Lazou Ahren I, Larsson N, Onning G. (2011) Randomised, double-blind and placebo-controlled study using new probiotic lactobacilli for strengthening the body immune defence against viral infections. *European Journal of Nutrition* 50, 203–210. doi:10.1007/s00394-010-0127-6

15 Cáceres P, Montes S, Vega N, Cruchet S, Brunser O, Gotteland M. (2010) Effects of Lactobacillus rhamnosus HN001 on acute respiratory infections and intestinal secretory IgA in children. *Journal of Pediatric Infectious Diseases* 5, 353–62.

16 de Vrese M, Winkler P, Rautenberg P, Harder T, Noah C, Laue C, *et al*. (2005) Effect of *Lactobacillus gasseri* PA 16/8, *Bifidobacterium longum* SP 07/3, B. *bifidum* MF 20/5 on common cold episodes: a double blind, randomized, controlled trial. *Clin Nutr.* 24, 481–91.

17 Guillemard E, Tanguy J, Flavigny A, de la Motte S, Schrezenmeir J, Guillemard E, *et al*. (2010) Effects of consumption of a fermented dairy product containing the probiotic *Lactobacillus casei* DN-114 001 on common respiratory and gastrointestinal infections in shift workers in a randomized controlled trial. *J Am Coll Nutr*. 29, 455–68.

18 Guillemard E, Tondu F, Lacoin F, Schrezenmeir J. (2010) Consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114001 reduces the duration of respiratory infections in the elderly in a randomised controlled trial. *Br J Nutr*. 103, 58–68. doi:10.1017/S0007114509991395

19 Hojsak I, Abdovic S, Szajewska H, Milosevic M, Krznaric Z, Kolacek S. (2010) Lactobacillus GG in the Prevention of Nosocomial Gastrointestinal and Respiratory Tract Infections. *Pediatrics* 125, E1171–E7. doi:10.1542/peds.2009-2568

20 Hojsak I, Snovak N, Abdovic S, Szajewska H, Misak Z, Kolacek S, *et al*. (2010) *Lactobacillus GG* in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: a randomized, double-blind, placebo-controlled trial. *Clin Nutr*. 29, 312–316. doi:10.1016/j.clnu.2009.09.008

21 Kekkonen RA, Vasankari TJ, Vuorimaa T, Haahtela T, Julkunen I, Korpela R. (2007) The effect of probiotics on respiratory infections and gastrointestinal symptoms during training in marathon runners. *Int J Sport Nutrition & Exercise Metabolism* 17, 352–363.

22 Kloster Smerud H, Ramstad Kleiveland C, Roll Mosland A, Grave G, Birkeland SE. (2008) Effect of a probiotic milk product on gastrointestinal and respiratory infections in children attending day-care. *Microbial Ecology in Health and Disease* 20, 80–85.

23 Rautava S, Salminen S, Isolauri E. (2009) Specific probiotics in reducing the risk of acute infections in infancy —a randomised, double-blind, placebo-controlled study. *Br J Nutr*. 101, 1722–1726. doi:10.1017/S0007114508116282

24 Turchet P, Laurenzano M, Auboiron S, Antoine JM. (2003) Effect of fermented milk containing the probiotic Lactobacillus casei DN-114001 on winter infections in free-living elderly subjects: a randomised, controlled pilot study. *J Nutrition, Health & Aging* 7, 75–77.

25 HTAi Interest Sub-Group on the Impact of Public Health interventions, special focus on Nutrition, on Health Outcomes Research and Measurement (INPHORM). http://www.htai.org/index.php?id=782. Accessed 24 March 2015

26 ISPOR Special Interest Group on medical nutrition products. http://www.ispor.org/sigs/MedicalNutrition.aspx. Accessed 24 March 2015.

27 Schlundt J. (2002) Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. FAO / WHO, Geneva.

28 Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, *et al*. (2014) Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 11(8):506–14. doi:10.1038/nrgastro.2014.66 PMID: 24912386

29 Lenoir-Wijnkoop I, Sanders ME, Cabana MD, Caglar E, Corthier G, Rayes N, *et al*. (2007) Probiotic and Prebiotic Influence Beyond the Intestinal Tract. *Nutrition Reviews* 65, 469–489.

30 Sanders ME, Lenoir-Wijnkoop I, Salminen S, Merenstein DJ, Gibson GR, Petschow BW, *et al*. (2014) Probiotics and prebiotics: prospects for public health and nutritional recommendations. *Ann. N.Y. Acad. Sci* 1309, 19–29. doi:10.1111/nyas.12377

31 Hao Q, Lu Z, Dong BR, Huang CQ, Wu T. (2011) Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev* 9, CD006895. doi:10.1002/14651858.CD006895.pub2

32 King S, Glanville J, Sanders ME, Fitzgerald A, Varley D. (2014) The Effectiveness of Probiotics on Length of Illness in Healthy Children and Adults who Develop Common Acute Respiratory Infectious Conditions: A Systematic Review and Meta-Analysis. *Br J Nutr.* 112(1), 41-54. doi:10.1017/S0007114514000075.

33 Kang EJ, Kim SY, Hwang IH, Ji YJ. (2013) The effect of probiotics on prevention of common cold: a meta-analysis of randomized controlled trial studies. *Korean J Fam Med*. 34(1), 2–10. doi:10.4082/kjfm.2013.34.1.2

34 Choix Méthodologiques pour l'évaluation économique à la HAS. Guide Méthodologique. Haute Autorité de la Santé. Saint Denis la Plaine. France. 2011.

35 Flahault A, Blanchon T, Dorléans Y, Toubiana L, Vibert JF, Valleron AJ. (2006) Virtual surveillance of communicable diseases: a 20-year experience in France. *Stat Methods Med Res*. 15(5), 413–21.

36 Gueyffier F, Strang CB, Berdeaux G, França LR, Blin P, Massol J, *et al*. (2012) Contribution of modeling approaches and virtual populations in transposing the results of clinical trials into real life and in enlightening public health decisions. *Therapie* 67, 367–374. doi: 10.2515/therapie/2012042

37 Eurostat website. http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/search_database. Accessed 24 March 2015

38 Fleming DM, Ayres JG. (1988) Diagnosis and patterns of incidence of influenza, influenza-like illness and the common cold in general practice. *J R Coll Gen Pract*. 38, 159–62.

39 Benseñor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE, *et al*. (2001) Active and passive smoking and risk of colds in women. *Ann Epidemiol*. 11, 225–231.

40 INSEE: National Institute for Statistics and Economic Studies. http://www.insee.fr/en/. Accessed 24 March 2015

41 Louhiala PJ, Jaakkola N, Ruotsalainen R, Jaakkola JJ. (1995) Form of day care and respiratory infections among Finnish children. *Am J Public Health* 85, 1109–12.

42 Jaakkola JJ, Heinonen OP.(1995) Shared office space and the risk of the common cold. *Eur J Epidemiol*. 11, 213–216.

43 Mosnier A. Place de la prescription antibiotique dans la prise en charge de la grippe. VIIème Journée Nationale des GROG—Paris, 21 novembre 2002. http://www.grog.org/documents/jour_2002/amm2.pdf. Accessed 24 March 2015

44 Cohen JM, Mosnier A, Grog I. (2003) A medical network to scrutinize Influenza epidemics ("La surveillance de la grippe en France"). *Médecine sciences* 19, 239–242. http://www.erudit.org/revue/ms/2003/v19/n2/000694ar.pdf. Accessed 24 March 2015

45 BdM-IT. Base des médicaments, informations tarifaires. www.ameli.fr. Accessed 24 March 2015

46 Cour des comptes. Les arrêts de travail et les indemnités journalières versées au titre de la maladie. 22/11/12—Rapport de la Cour des comptes juillet 2012. http://www.assemblee-nationale.fr/14/budget/mecss/cc-juillet2012.pdf. Accessed 24 March 2015

47 Grippenet résultats saison 2011–2012. https://www.grippenet.fr/fr/resultats/premiere-saison/. Accessed 24 March 2015

48 Vingilis E, Brown U, Hennen B. (1999) Common colds. Reported patterns of self-care and health care use. *Can Fam Physician* 45:2644–6, 2649–52.

49 Bramley TJ, Lerner D, Sames M. (2002) Productivity losses related to the common cold. *J Occup Environ Med.* 44, 822–829.

50 Pitman RJ, Nagy LD, Sculpher MJ. (2012) Cost-effectiveness of childhood influenza vaccination in England and Wales: Results from a dynamic transmission model. *Vaccine* 31(6):927–42. doi:10.1016/j.vaccine.2012.12.010

51 Baguelin M, Flasche S, Camacho A, Demiris N, Miller E, Edmunds WJ. (2013) Assessing optimal target populations for influenza vaccination programmes: an evidence synthesis and modelling study. *PLoS Med.* 10(10):e1001527. doi:10.1371/journal.pmed.1001527

52 Viboud C, Boëlle PY, Cauchemez S, Lavenu A, Valleron AJ, Flahault A, *et al*. (2004) Risk factors of influenza transmission in households. *Br J Gen Pract*. 54(506):684–9.

53 Busse PJ, Mathur SK. (2010) Age-related changes in immune function: effect on airway inflammation. J *Allergy Clin Immunol*. 126(4):690–9; quiz 700–1. doi:10.1016/j.jaci.2010.08.011

54 Jefferson T, Del Mar CB, Dooley L, Ferroni E, Al-Ansary LA, Bawazeer GA, *et al*. (2011) Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database of Syst Rev*. 7, CD006207.

Chapter 9.2

The clinical and economic impact of probiotics consumption on respiratory tract infections: projections for Canada

Irene Lenoir-Wijnkoop, Laetitia Gerlier, Denis Roy, Gregor Reid

Published in: PLoS One 2016;11(11), e0166232

ABSTRACT

Introduction There is accumulating evidence supporting the use of probiotics, which are defined as "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host", as a preventive measure against respiratory tract infections (RTI). Two recent meta-analyses showed probiotic consumption (daily intake of 10^7 to 10^{10} CFU in any form for up to 3 months) significantly reduced RTI duration, frequency, antibiotic use and work absenteeism.

Objectives The aim of this study was to assess the impact of probiotic use in terms of number of RTI episodes and days averted, and the number of antibiotic prescriptions and missed workdays averted, in the general population of Canada. In addition, the corresponding economic impact from both a healthcare payer and a productivity perspective was estimated.

Methods A microsimulation model was developed to reproduce the Canadian population (sample rate of 1/1000 = 35 540 individuals) employing age and gender. RTI incidence was taken from FluWatch consultation rates for influenza-like illness (2013–14) and StatCan all-cause consultations statistics. The model was calibrated on a 2.1% RTI annual incidence in the general population (5.2 million RTI days) and included known risk factors (smoking status, shared living conditions and vaccination status). RTI-related antibiotic prescriptions and work absenteeism were obtained from the literature.

Results The results indicate that probiotic use saved 573 000–2.3 million RTI-days, according to the YHEC–Cochrane scenarios respectively. These reductions were associated with an avoidance of 52 000–84 000 antibiotic courses and 330 000–500 000 sick-leave days. A projection of corresponding costs reductions amounted to Can$1.3–8.9 million from the healthcare payer perspective and Can$61.2–99.7 million when adding productivity losses.

Conclusion The analysis shows that the potential of probiotics to reduce RTI-related events may have a substantial clinical and economic impact in Canada.

INTRODUCTION

Respiratory tract infections (RTI) are highly contagious infections of the sinus, throat, or airways. Typically viral, these self-limiting infections can last up to 2 weeks and vary in severity.[1] Influenza-like-illness (ILI) and influenza are common RTIs, and are defined as acute onset of respiratory symptoms (*i.e.* cough, sore throat or shortness of breath), accompanied by fever, headache and/or myalgia.[1-3] Cases of laboratory-confirmed influenza virus are termed 'influenza'.[1]

Due to their high incidence, RTIs carry a heavy burden on society and the healthcare systems. Approximately 5–20% of the population will have at least one RTI annually, resulting in 31.4 million outpatient visits, 3.1 million hospitalized days, and 41 000 deaths each year in the USA.[4] ILI and influenza are estimated to result in 3–5 million illnesses and 250 000–500 000 deaths annually, around the world.[5] In Canada, 14 000–17 000 hospitalizations (8–10% of all hospital admissions)[6] and 3 500 deaths are attributed to influenza each year.[7] The estimated total annual economic burden of RTIs in Canada in 2008, was Can$5.4 billion, representing 2.9% of all healthcare costs.[2,8]

Treatment of RTIs relies mainly on symptom control, however, despite being most commonly of viral etiology, they often lead to the prescription of antibiotics.[9,10] The use of antiviral agents within 48 hours of illness onset reduces the duration of symptoms by about 1 day; however their effectiveness might be limited by side effects and resistance.[11-14] In the absence of satisfactory treatments, prevention is the cornerstone of influenza management.[1,14] In addition to limiting contact and frequent hand washing,[15] the mainstay of prevention against influenza infection is vaccination.[1,14] Although influenza is considered to be a vaccine preventable disease, vaccine effectiveness can be limited by mismatches with the circulating viral strains[14] and low uptake in the population.[16]

Probiotics, defined as "live micro-organisms which, when administered in adequate amounts, confer a health benefit on the host",[17] are being consumed with increasing frequency over the past ten years. There is accumulating evidence supporting the use of probiotics, both in food products and nutritional supplements, as a preventive measure against RTIs.[18-24] Two recent meta-analyses by the York Health Economics Consortium (YHEC) and the Cochrane Collaboration,[18,20] showed that probiotic consumption reduced RTI duration by 0.8 days[20] and 1.9 days[18] respectively. Moreover, they reduced the incidence of RTIs by 47%,[18] the antibiotic prescription rate by 35%[18] and absenteeism by 17%.[20]

We hypothesize that there are potential benefits to the Canadian healthcare system associated with these reductions in RTI incidence and duration, which may contribute in lightening the burden of an increasing scarcity of resources.

OBJECTIVE

The primary objective of this study was to assess the clinical impact of probiotics use projected to Canada: number of RTI episodes and RTI days averted, number of RTI-related antibiotics prescriptions and missed work days averted. Our secondary objective was to estimate the related economic impact from a healthcare payer perspective and a productivity perspective.

METHODS

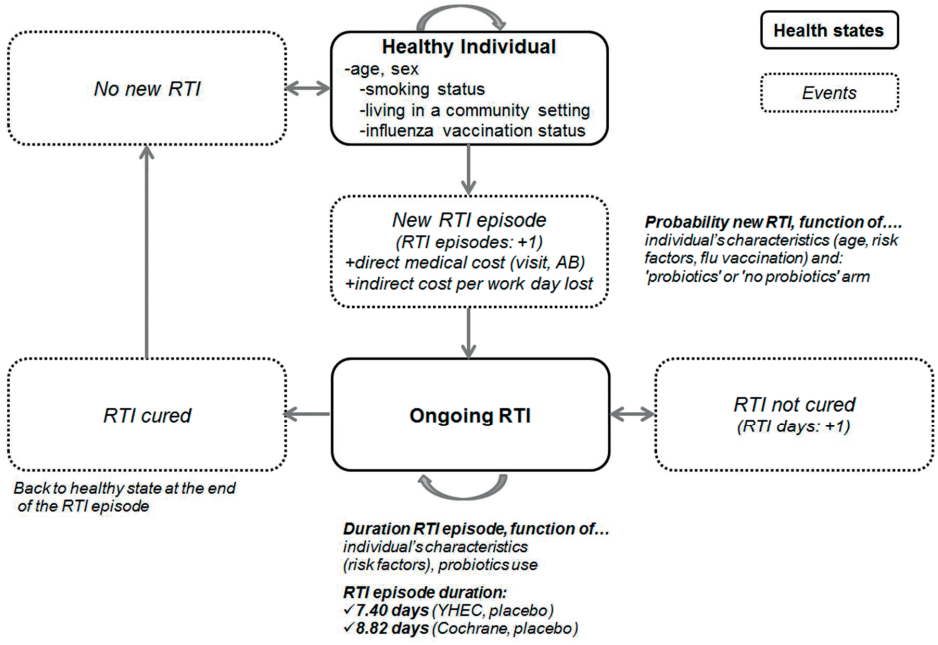
An individual-based model was used to perform a health-economic assessment comparing health outcomes and costs with or without probiotics consumption for the population of Canada. Ethics approval and informed consents were not required for this modeling study.

Model structure

A state-transition microsimulation model, originally applied to the French healthcare setting,[25] was adapted to the Canadian population. An important aspect of this adaptation from the French model is the incorporation of the influenza vaccination status of the Canadian population. The model compared the impact of probiotic consumption *vs.* no probiotic consumption, using a 1-day cycle, over a time horizon of 365 days, covering the annual surveillance period of flu in Canada from September 2013 to August 2014. The year 2013–2014 was chosen out of the 3 annual surveillance periods from 2012–13 to 2014–15, as the 2013–14 epidemic was of medium intensity.[26]

A sampling rate of 1/1000 virtual healthy individuals, representative of the Canadian population in terms of age and gender was entered into the model. Each subject was concurrently assigned to two arms 'generalized probiotics use' and 'no probiotics use'. Movement from the 'healthy' state to an 'RTI' state was based on daily age-specific RTI incidence rates adjusted for the following risk factors: smoking status, living in community setting and influenza vaccination status. Individuals remained in a 'RTI' state until RTI episode resolution and then returned to the 'healthy' state (Figure 1).

Figure 1. Schematic state-transition model representation



Legend:
AB: antibiotics; RTI: respiratory tract infection;
YHEC: York Health Economics Consortium

Since RTIs as a whole are not subject to herd immunization because of their multi-strain viral origin, the probability of having a new RTI is independent from the number of previous RTIs. Hospitalization and mortality were not incorporated into the model as our scope was restricted to the primary care setting.

The TreeAge Pro 2015 software (TreeAge Software Inc., Williamstown, MA) was employed to conduct the model analyses.

Model outcomes

The main outcomes of the simulation were the number of RTI events, occurring between September 2013 and August 2014, RTI duration in number of days, number of antibiotic courses prescribed, number of missed work-days due to RTI, direct medical costs (*i.e.* physician visits, prescribed antibiotics and non-antibiotics drugs) and indirect costs (*i.e.* productivity loss) from September 2013 to August 2014. The differences between the 'probiotic' arm and the 'no probiotic' arm in number of events and costs were calculated according to two scenarios based on two meta-analyses, conducted respectively by the YHEC and Cochrane groups.[18,20]

Perspective

Two perspectives were used in the model: a 'healthcare payer' (HCP) perspective, which included RTI-related medical expenses for both public and private payers, and a 'productivity' perspective, which focused on productivity losses due to time absent from work.

Model inputs

A summary of model inputs can be found in Tables 1 and 2.

Demographic data

In 2014, the total Canadian population was 35 540 000 individuals, and was reported by gender and 5-year age increments.[27]

RTI incidence

The type of RTIs included in this model were ILIs, as reported by FluWatch,[28] Canada's national surveillance system that monitors the spread of epidemics. The FluWatch program collects data from a network of labs, hospitals, doctor's offices and provincial and territorial ministries of health and includes only patients who have consulted with a physician for an ILI, and therefore, represents a subset of all patients with ILIs in Canada.[29] ILIs as defined by FluWatch ("acute onset of respiratory illness with fever and cough and with one or more of the following—sore throat, arthralgia, myalgia, or prostration which is likely due to influenza")[29] are included in the definitions of RTIs symptoms used in the Cochrane ("common cold and inflammation of the trachea and larynx, with symptoms including fever, cough, pain and headaches")[18] and YHEC ("colds or influenza-like symptoms")[20] meta-analyses. Both meta-analyses included studies of patients with acute RTIs similarly defined, however, they also included patients with common cold, thus, our criteria were more restrictive.

In the absence of published Canadian absolute ILI incidence, the incidence of RTIs was calculated and derived from the weekly ILI consultation rate per 1000 physician visits in the general Canadian population,[26] by age group, for the years 2012–13, 2013–14 and 2014–15 (Table 1).

The number of all-cause physician visits was estimated from the Statistics Canada website (number of individuals with ≥ 1 physician contact per year, per age group[30] assuming a single contact per year per consulting individual. For model purposes, the all-cause consultations were assumed to be uniformly distributed over the year and the consultation rate among 0–12 year age group was assumed equal to that among ≥ 65 year age group.[31]

Table 1. Summary of model inputs – Epidemiological parameters, base case Canada

Model parameters	Value	Reference
Season start-end	Sep 2013-Aug 2014	FluWatch
Time horizon (days)	365	FluWatch
Canada population size	35,154,279	StatCan 2014
Risk factors	**% Population**	
Active smoker		OFDT 2010
Men, 15-49y	19.5%	StatCan, Tab 105-0501
Men, 50+	9.3%	StatCan, Tab 105-0501
Women, 15-49y	12.0%	StatCan, Tab 105-0501
Women, 50+	7.9%	StatCan, Tab 105-0501
Passive smoker	16%	StatCan, Tab 105-0501
Living in a community setting		
Pre-school children (0-4)	60%	StatCan
Students (5-15)	100%	UNICEF 2012
Employment rate adults:		
Adults, 15-24y	55.5%	StatCan, Tab 282-0002
Men 25-44y	85.3%	StatCan, Tab 282-0002
Men 45-64y	75.3%	StatCan, Tab 282-0002
Women 25-44y	56.9%	StatCan, Tab 282-0002
Women 45-64y	77.5%	StatCan, Tab 282-0002
Working in open-space offices	70.0%	IFMA (US)
Adults in retirement home, 65-74y	11.0%	StatCan, GSS 2011
Adults in retirement home, 75-84y	35.0%	StatCan, GSS 2011
Adults in retirement home, 85+	55.0%	StatCan, GSS 2011
Influenza vaccination coverage		
Children, 0-12y	23%	StatCan
Children, 12-17y	23%	StatCan
Adults, 18-34y	17%	StatCan
Adults, 35-44y	22%	StatCan
Adults, 45-54y	25%	StatCan
Adults, 55-64y	39%	StatCan
Adults, 65y+	64%	StatCan
Use of probiotics in Canada		
Overall	Heavy/regular users: 34%/10.7%	IPSOS survey
Male	Regular/heavy users: 23%/7.1%	US survey
Female	Regular/heavy users: 45%/14.2%	US survey
Steps to RTI incidence estimation		
Number of all-cause MD visits:		
≥ 1 all-cause physician visits, age 12+	N=23,263,508 (759.69 /1000 persons)	StatCan
≥ 1 all-cause physician visits, all ages	N=26,936,522 (766.24 /1000 persons)	StatCan + assumption*

Table 1. Summary of model inputs – Epidemiological parameters, base case Canada (*continued*)

Model parameters	Value	Reference
	Total ILI Consultations (ILI consultation rate)	
Total ILI consultations 2012-13	561,771 (1,664 /100,000 persons)	Calculation (FluWatch + StatCan)
Total ILI consultations 2013-14 (base case)	735,967 (2,094 /100,000 persons)	Calculation (FluWatch + StatCan)
Total ILI consultations 2014-15	789,710 (2,222 /100,000 persons)	Calculation (FluWatch + StatCan)
RTI duration	**Duration (days)**	
Without probiotics (placebo)	YHEC: 7.40/Cochrane: 8.82	King *et al* 2014, Hao 2015
Impact of risk factors on RTI		
Active smoker	On RTI incidence: NA/On RTI duration: +4.5% *vs*. no smokers	Benseñor 2001
Passive smoker	On RTI incidence: RR=1.15 *vs*. no smokers/ On RTI duration: +16.8% *vs*. no smokers	Benseñor 2001
Living in a community setting:		
Day care (e.g. school) vs. home care	On RTI incidence: RR=1.22 On RTI duration: NA	Louhiala 1995
Shared office vs. alone	On RTI incidence: RR=1.07# On RTI duration: NA	Jaakkola 1995
Impact of using probiotics		
YHEC	On RTI incidence: NA/On RTI duration: -0.77 days *vs*. pbo [-0.04;-1.50]/On antibiotics use: NA/On work absenteeism: -0.17 SMD [-0.31;-0.03]	King *et al.* 2014
Cochrane	On RTI incidence: RR=0.70 *vs*. pbo [0.50;0.84] ##/On RTI duration: -1.89 days *vs*. pbo [-2.03;-1.75]/On antibiotics use: RR=0.65 *vs*. pbo [0.45;0.94]/On work absenteeism: NA	Hao *et al.* 2015

IFMA: International Facility Management Association; MD: Medical doctor; NA: not applicable; pbo: placebo; SMD: standardized mean difference

* Assumes same visit rate in <12 years and 65+ years

#OR = 1.64

##OR = 0.53 [0.37;0.76]. Conversions into RR using exact numbers of events and sample sizes

Effect of probiotics on RTI

Two scenario analyses were conducted independently, using the results from the two meta-analyses. Both scenarios are thus based on different assumptions. In the first scenario, using the data reported by YHEC,[20] the estimated impact of probiotics was based on an average RTI duration of 7.40 days and a reduction of duration of -0.77 days [-1.50, -0.04]. The second scenario, using the Cochrane data[18] was based on an average RTI duration of 8.82 days, a reduction of duration of 1.89 days [-2.03, -1.75] and a reduced

risk of an RTI incidence of 0.70 among non-vaccinated individuals only (in line with the inclusion criteria of this meta-analysis). Both scenarios additionally used a reduced risk of receiving an antibiotic prescription per RTI episode of 0.65, among non-vaccinated individuals only, and reduced absenteeism of 0.87 and 0.26 days among adults and children, respectively.

Currently, an estimated 12% of the Canadian population regularly consumes probiotics. This consumption rate was used to adjust the RTI incidence and duration per RTI episode of the general population in the model. The percentage of Canadians currently consuming probiotics was estimated from two sources: a recent survey on health product consumption in the overall Canadian population and a US study reporting the ratio of men and women using probiotics, resulting in an estimated 8% of men and 15% of women (and 12% overall) as regular consumers of probiotics.[32,33]

Resource use and costs

For each RTI consultation, the cost of one visit to the family physician was attributed at a unit cost of Can$32.[34] It was assumed that 90% of the consulting RTI patients take over-the-counter analgesic or anti-pyretic medications, at a unit cost of Can$6.29 for 7 days of treatment with ibuprofen.[35] In Canada, an estimated 26.1% of consulting RTI patients are prescribed antibiotics for RTI at a unit cost of Can$25.00 per antibiotic course.[36] In terms of reimbursement from public HCP sources, the visit cost is fully covered, while the public insurers covered an estimated 30% of antibiotic prescriptions in 2012/2013.[37] Pain/fever medications are assumed to be self-medication, out-of-pocket expenses for the patient. Resource costs are presented in Table 2.

The cost of probiotics was not incorporated into this projection. Firstly, the study aimed at assessing the benefits of routine probiotics consumption. In addition, probiotic products, whether they are part of daily food consumption or purchased in the form of nutritional supplements, are not reimbursed by the healthcare system, and thus fall beyond the scope of the study perspective (HCP and productivity losses). This point is further addressed in the discussion. The heterogeneity of the types of commercialized probiotics and the lack of available data on consumer habits, make it difficult to quantify the type, amount and cost of probiotics consumed.

Indirect costs included the productivity losses caused by the working days lost due to RTI. In the absence of Canadian specific data, estimates were derived from a US study which reported the number of missed working days caused by RTI, among employed adults for their own illness and illness of their children.[38] The cost of 1 day of lost productivity was estimated at Can$182, based on the Canadian gross domestic product

(GDP) per capita divided by 250 working days per year. All costs were obtained from Canadian sources and are expressed in 2016 Canadian dollars.

Table 2. Summary of model inputs–Resource utilization and costs parameters, base case Canada (2015 costs)

Direct cost parameters	**% using the resource**	**Number, mean**	**Unit cost (% paid by public payer)**	**Reference**
GP visits in case of RTI	100%	1 visit	Can$32.00 (100%)	Family Health Online Canada
Analgesic/anti-pyretic in case of RTI	90%	1 pack for 7 days	Can$6.29 (0%)	Well.ca
Antibiotics course, in case of RTI	26.1%	1 course of 10 days	Can$25.00 (30%)	Kwong *et al.* 2009, Canadian RX atlas
Indirect cost parameters	**% missing days**	**Number of missed days, mean**	**Cost per day lost (Employer cost)**	**Reference**
employee with RTI	42.0%	1.7 days	Can$181.61	Palmer *et al.* 2010, GDP per capita
sick children with RTI	18.0%	0.5 days	Can$181.61	Palmer *et al.* 2010, GDP per capita

Can$: Canadian Dollar
GDP: gross domestic product
GP: general practitioner
ILI: influenza-like illness
RTI: respiratory tract infection

RTI risk factors

In the model, RTI incidence and/or duration were adjusted for known risk factors of smoking status, living in a community setting status (*i.e.* child attending day care or school, employed adults working in open offices, or elderly in a retirement home) and influenza vaccination status. The risk factor probabilities used in the model and their impact on RTI are reported in Table 1.

Smoking status

A study based on randomized controlled trial data showed that active smokers were more likely to report a prolonged RTI episode (> 7 days *vs*. 1–3 days) compared to never smokers: light smokers (<25 cigarettes a day) had a relative risk of 1.62 [1.40,1.87] and heavy smokers (≥ 25 cigarette a day), had a risk of 2.63 [2.02, 3.44].[39] Non-smokers exposed to second hand cigarette smoke also reported a longer duration of upper RTI (RR = 1.12 [0.99, 1.27]) *vs.* never smokers. From these RR, the average RTI duration was estimated to be 16.8% [9.1%, 25.2%] longer for active smokers and 4.5% [0.1%, 8.9%] longer for passive smokers, compared to never smokers (Table 1). In addition, RTI incidence was assumed to be higher among passive smokers (RR = 1.15 [1.05, 1.26]) *vs.*

never smokers (Table 1). The proportion of active[40] and passive smokers[41] in Canada, by age group and sex, was obtained from Statistics Canada.

Living in a community setting

The relative risk of an RTI event among children attending day care *vs.* home care (RR = 1.22 [1.13, 1.31]) was applied to children aged 0–4 years attending day care and children aged 5–15 years attending school *vs.* children staying at home (Table 1).[42] For employed adults aged 16–64 years old working in a shared office and elderly people aged above 65 living in a retirement home, an increased risk of RTI (RR = 1.07[1.01;1.13]) was applied.[43] The proportion of Canadians living in a community setting, by age group, was obtained from Statistics Canada.

Influenza vaccination

Two recent systematic reviews on influenza vaccination reported decreased risks of ILI among vaccinated adults (RR = 0.83 [0.78, 0.87])[44] and children (RR = 0.64 [0.54, 0.76],[45] which were applied in the model given that our RTI events are matching the ILI definition (Table 1) Since vaccination against influenza is recommended for everyone 6 months of age and older in Canada,[46] the probiotic effects estimated from the Cochrane meta-analysis were not applied to individuals in our model who were vaccinated against influenza, to keep in line with the inclusion criteria of the Cochrane meta-analysis; under the YHEC scenario RTI rates were adjusted for vaccination status. The proportion of Canadians who were vaccinated for the 2013–14 season were obtained from the 2015 Canadian Community Health Survey.[47]

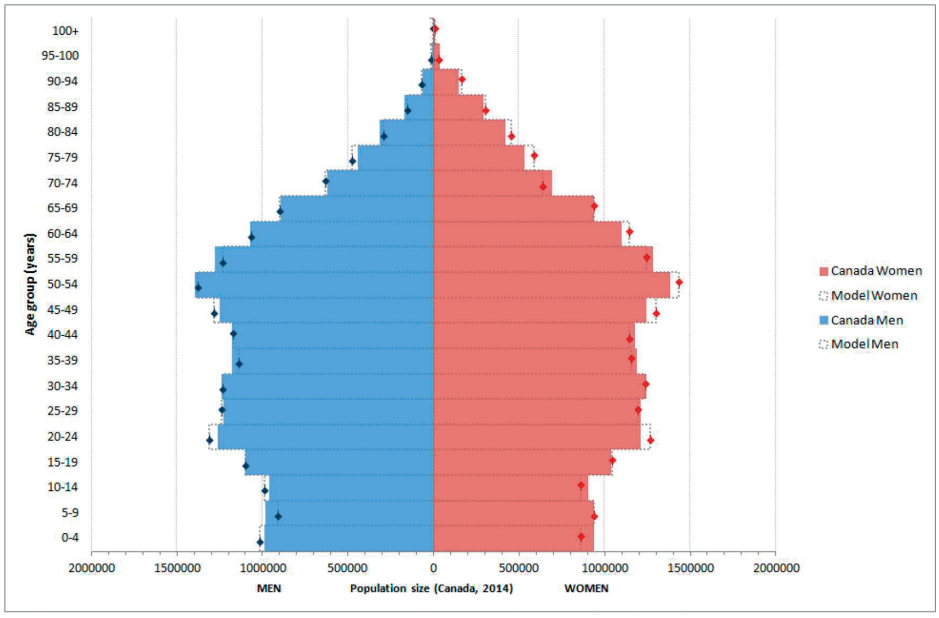
Analyses

The model population was analyzed using SAS software (SAS Institute, Cary, North Carolina) and results are presented for 35 540 individuals (model sampling rate 1/1000). One-way sensitivity analyses to assess uncertainty around the results were performed on the preceding (2012–13) and following (2014–15) influenza seasons, which had slightly lower and higher RTI rates, respectively, and across the lower and upper 95% confidence limits for reduced duration of RTI and reduced incidence of RTI.

RESULTS

A sampling rate of 1/1000, or 35 540 simulated individuals, reproduced the Canadian population structure in terms of age and gender (Figure 2), with an error rate less than 5% between expected population size and modeled population size.

Figure 2. Canada population structure by age and gender, from national statistics (colored bars) *vs.* simulated population (dotted line bars)



Model results for season 2013-14 were compared to Canada population data of 2014 (StaCan)

Under the YHEC scenario, which focused on the probiotic effect on RTI duration, projected to the Canadian population over a one year period (Sept 2013 –Aug 2014), probiotic consumption would avert 572 629 days of RTI illness (10.4% reduction), 51 526 antibiotic prescriptions for RTI (26.4% reduction) and 329 977 days of missed work (35.9% reduction), compared to no probiotic consumption (Figure 3). Under the Cochrane scenario, which focused on the effect of probiotics on reducing both RTI incidence and duration, over the same time period and projected to the Canadian population, probiotics consumption would avert 2 329 800 RTI days (35.3% reduction), 180 000 RTI episodes (23.9% reduction), almost 84 272 antibiotics prescriptions for RTI (42.8% reduction) and 500 228 missed work days (51.3% reduction), compared to no probiotic consumption (Figure 3).

In terms of economic impact, the cost reduction associated with the averted RTI events amount to Can$1.29 million from the HCP perspective and Can$61.22 million when taking productivity losses into account (-30.6%), based on YHEC scenario (Figure 4).

In the Cochrane scenario, the economic impact of averted RTI events was estimated at Can$8.89 million from the HCP perspective and Can$99.77 million when productivity losses are included (Figure 4). A higher relative benefit of probiotic consumption

Figure 3. Prevented RTI-related events with *vs.* without probiotics according to two scenarios

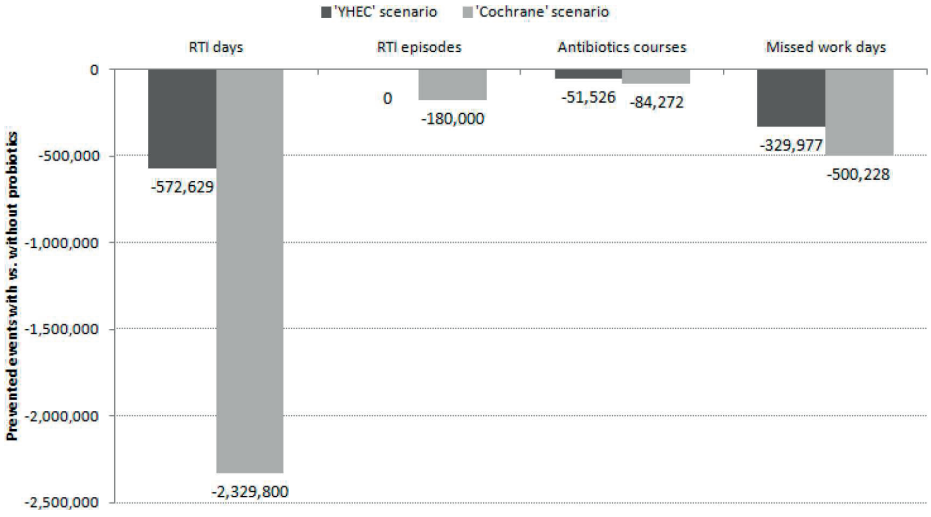
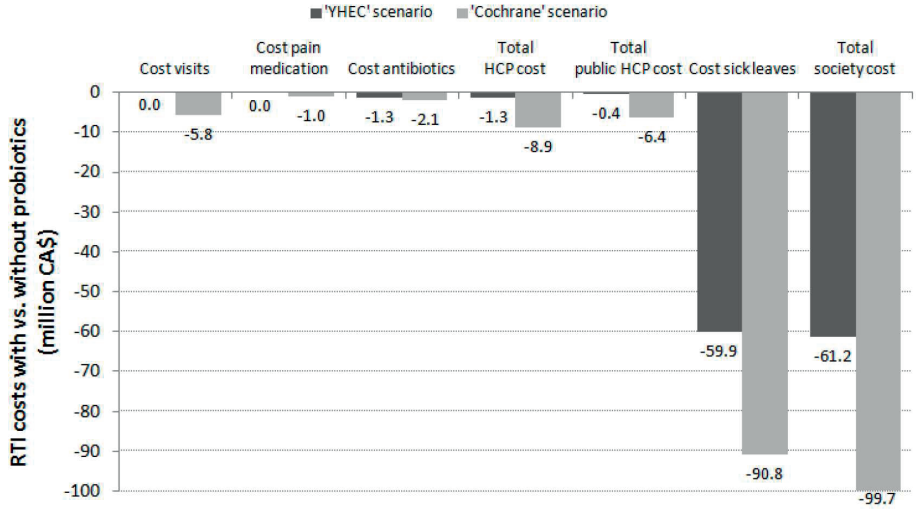


Figure 4. Savings with *vs.* without probiotics according to two scenarios



on the reduction of RTI duration was observed among children <10 years old, on individuals living in a community setting and on those who were not vaccinated against influenza. Children <10 years old represented 10.5% of the population (N = 3 721 000) but accounted for 19.5% of the potentially averted RTI days (-111 650 days), thus, this young age group shows a higher incremental benefit than other age groups. Individuals working or living in a community setting accounted for 50.7% (N = 18 000 000) of the total population but accounted for 56.8% (-325 459 days) of the total RTI-days saved

with probiotics consumption. Non-vaccinated individuals represented 69.4% of the total Canadian population in 2014, these individuals accounted for 74.5% of the total RTI-days potentially averted in the general population under the YHEC scenario, meaning that even vaccinated individuals can have some benefits of probiotics.

The results of the sensitivity analyses showed that the model results are robust against varying RTI rates from the preceding (2012–13) and following (2014–15) seasons, and the lower and upper 95% confidence limits of RTI duration and RTI incidence. The impact of probiotic consumption on RTI days based on 2012–13 and 2014–15 seasons did not differ substantially from the base case results. Averted RTI days ranged from 465 080 to 582 890 in the YHEC scenario (corresponding HCP costs of averted RTI events Can$1.07–1.33 million and Can$50.63–63.76 million when including productivity losses), and from 1.62 to 2.42 million days in the Cochrane scenario (corresponding HCP costs of averted RTI events Can$5.87–8.99 million and Can$70.44–103.17 with productivity losses).

Applying the lower and upper 95% confidence limits of the reduction of RTI duration from the YHEC meta-analysis (-0.04 to -1.50 days per episode), the potentially averted RTI days in the probiotic arm varied between 29 720 and 1.12 million days from the Cochrane meta-analysis (-2.03 to -1.75 days per episode), the potentially averted RTI days in the probiotics arm varied between 2.27 and 2.38 million.

When testing the 95% CI around the reduction of RTI incidence from the Cochrane meta-analysis (RR from 0.50 to 0.84), the averted RTI days in the probiotics arm varied between 1.67 and 2.92 million days.

DISCUSSION

The microsimulation described here estimates the potential clinical and economic benefits of probiotic consumption on RTIs in Canada, under two distinct scenarios derived from two recent meta-analyses.[18,20] The model was anchored on the Canadian population structure and RTI incidence data were applied. Projecting the clinical benefits onto the Canadian population demonstrates that probiotic consumption has the potential to save 180 000 RTI episodes and 500 000–2.3 million RTI-days with an associated avoidance of 50 000–85 000 antibiotic courses and 300 000–500 000 work absenteeism days. These averted RTI events, when translated into averted costs for the HCP, would represent Can$1.3–8.9 million and up to Can$61.2–99.7 million when including the averted costs of productivity losses.

Our findings are consistent with a similar analysis conducted on the French population, which showed that population level probiotic consumption in France would potentially save 2.4–6.6 million RTI sick days, 291 000–473 000 antibiotic courses and 581 000–1.5 million work absenteeism days. The economic impact of preventive probiotic use was estimated to be €14.6 - €37.7 million to the French National Health Care System.[25] The main reason for a higher probiotic impact in the French analysis is that the RTI definition was encompassing not only ILI but also common colds. Data on common colds were indeed not available for the Canadian population, therefore only ILIs were included in the model, resulting in a more restrictive inclusion. As well, unlike the French model, the impact of confounding due to vaccination against influenza was decreased in the Canadian model by including the vaccination status of the population. Both of these factors led to a more conservative model.

As in the French model, the Canadian model shows a higher incremental benefit of probiotic consumption among children <10 years old and individuals living in a community setting. This is likely due to a higher incidence of ILIs among children[48] and the ease of transmission among individuals who go to school and work in close proximity to others.[42,43] The Canadian model also shows higher benefit among people not vaccinated against influenza.

In both French and Canadian analyses, the acquisition cost of probiotics was not included since probiotics are purchased on a voluntary basis by the families without any subsidy or reimbursement, independent of their health status. As such, the cost of probiotics is not part of the HCP perspective adopted in our study. The particularity of probiotics, and healthy/functional food in general, compared to a standard health intervention is that individuals can decide to acquire probiotics for several reasons (taste/preference over non-fermented dairy products, healthier diet purpose, ...) and the potential RTI prevention properties might only be part of it. From the large Canadian survey on healthy food,[32] the average household budget for such products in heavy *vs* light users is Can$175 *vs.* Can$128 per week *i.e*. an incremental weekly expense of Can$47 for heavy users. This might represent the willingness to pay (WTP) of Canadian households for healthy food including probiotics. In comparison, the cost of probiotics in France per household was estimated between Can$182 and Can$484 for a period of 7 months *i.e*. Can$7–17 per week. This suggests that the acquisition cost of probiotics is largely inferior to the WTP for healthy food, and this without any incentives (aside private advertising). Other out-of-pockets expenses that were not included in this model due to lack of data were over-the-counter (OTC) medication and costs related to informal care for a sick parent or child. The above-mentioned costs would be part of a so-called 'society' perspective, along with any Government expenses on campaigns or

advertisements to, for example, encourage healthy lifestyle choices in the population. However, this fell beyond the scope of our analysis.

Importantly, the current incidence data were representative of individuals consulting a GP for their RTI. They represent only a very small proportion of RTI sufferers, and therefore, the real savings may be higher than reported.

The role of functional foods is increasingly being recognized as important, by not only public health departments, but also by payers and policymakers.[49] Epidemiological studies have established the clinical benefits of nutrition and functional foods on disease, including the use of probiotics to prevent diseases.[50] Several meta-analyses of randomized controlled trials have shown a benefit of probiotic interventions in various therapeutic areas including neonatology,[51] gastroenterology,[52] cardiovascular risk factors,[53] urinary[54] and respiratory tract.[18,20] Along with the clinical benefits, functional foods have the potential to impact healthcare costs. In the current context of competing healthcare dollars, with the challenge of allocating limited funds to an extensive list of needs, functional food –including probiotics– offers an attractive population-based strategy for improving health. The emerging discipline of nutrition economics,[55] to which this study contributes, will help decision makers to evaluate the relevance of assessing the economic impact of nutrition.[49]

This analysis shows that increasing probiotic consumption is likely to have substantial positive consequences, not only on the healthcare system, but also on work absenteeism of sick employees per se, as well as those absent because of their children with respiratory illness. This is meaningful, as approximately one third of employees working in an open office plan confirm their working environment puts them at increased risk of illness due to the close and open contact with colleagues.[56] The impact of RTI on work presenteeism (reduced on-the-job productivity due to RTI symptoms) could be another field of research to cover.

Limitations

Our research is subject to the limitations inherent to all modelization work, and uncertainty around model inputs in particular. First of all, both meta-analyses highlighted important heterogeneity in the included studies. In addition, the meta-analyses of Cochrane are more cautious with regards to the results, qualifying the evidence as “low quality” while YHEC concludes that their results are based on “a number of good quality RCTs”. In our analysis, we decided to show both scenarios to cover both more optimistic effects based on ‘low quality evidence’ (Cochrane) and more conservative effects based on a higher quality of evidence (YHEC). We acknowledge that the evidence around the

preventive effects of probiotics is deemed preliminary by a number of scientists, in view of contradictory results: non-conclusive subgroup analyses by age group (YHEC) or efficacy not sufficiently ascertained according to Caffarelli *et al*,[57] while two other meta-analyses including moderate quality[58] to high-quality[59] studies confirm the positive effect of probiotics on RTI incidence and symptoms.

Despite practical or ethical challenges, it is expected that the quality of RCTs conducted in the nutrition area will substantially improve in the near future.[60,61] Another limitation of our work concerns the RTI definitions and labels used in the meta-analyses, which are approximations of the ILI infections as defined by FluWatch; the overlap was deemed acceptable though.

Furthermore, seasonality data of all-cause visits was not available from Statistics Canada, therefore an average number of weekly all-cause visits was assumed throughout the year, based on the rate of individuals who had at least one visit to a health care professional in the past 12 months. This is most likely a very conservative assumption as we counted a single all-cause visit per consulting patient (in the US, the average is around 3 visits per person-year). And lastly, because Statistics Canada does not report the all-cause consultation rate on the population <12 year old, we assumed this age group was equal to the ≥65 year age group in terms of visit rate, as was observed in the US statistics.[62] These modifications can artificially inflate or deflate the RTI incidence at various points during the year. These limitations may have consequences on the model outcomes when examined by subgroup, as we assumed that risk factor prevalence and effects were independent. The overall impact on the Canadian data is not considered to be high, as the model remained correctly anchored on national statistics, for 3 years in a row. In terms of economic results, there is some uncertainty around the duration of ILI symptoms potentially requiring medications; package size of analgesics/antipyretics was estimated based on the duration of RTI episodes in the placebo groups of the meta-analyses (7–8 days) while the cost of an antibiotic course was directly provided by a Canadian health information website.

CONCLUSION

This study shows the potential for a substantial reduction of RTI events and related HCP costs and productivity losses if probiotics would be consumed routinely at a population level in Canada. The model projects a higher relative benefit of probiotic consumption among children <10 years old, individuals living in a community setting and those not

vaccinated against influenza. Further good quality, prospective research on probiotics effectiveness is required to refine our preliminary projections.

REFERENCES

1 World Health Organization. Influenza (Seasonal) Fact sheet N°211 2014 http://wwwwhoint/mediacentre/factsheets/fs211/en/. Accessed 4 March 2016

2 Government of Canada. Influenza Definitions. http://healthycanadians.gc.ca/diseases-conditions-maladies-affections/disease-maladie/flu-grippe/surveillance/season-definitions-saison-eng.php—a. Accessed 4 March 2016

3 European Center for Disease Prevention and Control. Available at: http://ecdc.europa.eu/en/healthtopics/influenza/surveillance/Pages/influenza_case_definitions.aspx. Accessed 4 March 2016

4 Molinari N, Ortega-Sanchez I, Messonnier M, Thompson W, Wortley P, Weintraub E, *et al*. (2007) The annual impact of seasonal influenza in the US: measuring disease burden and costs. *Vaccine* 25(27), 5086–96. doi:10.1016/j.vaccine.2007.03.046

5 World Health Organization. Influenza Fact Sheet. 2003. http://www.phac-aspc.gc.ca/im/nics-enva/vcac-cvac-eng.php. Accessed 4 March 2016

6 Schanzer D, Langley J, Tam T. Role of influenza and other respiratory viruses in admissions of adults to Canadian hospitals. (2008) *Influenza and Other Respiratory Viruses* 2(1), 1–8. doi:10.1111/j.1750-2659.2008.00035.x

7 Schanzer DL, Sevenhuysen C, Winchester B, Mersereau T. (2013) "Estimating Influenza Deaths in Canada, 1992–2009." *PLoS One* 8(11), e80481. doi:10.1371/journal.pone.0080481

8 Public Health Agency of Canada. Economic Burden of Illness in Canada, 2005–2008. http://wwwphac-aspcgcca/publicat/ebic-femc/2005-2008/assets/pdf/ebic-femc-2005-2008-engpdf. Accessed 4 March 2016. 2014

9 Vervloet M, Meulepas M, Cals J, Eimers M, Van der Hoek L, Van Dijk L. (2016) Reducing antibiotic prescriptions for respiratory tract infections in family practice: results of a cluster randomized controlled trial evaluating a multifaceted peer-group-based intervention. *NPJ Prim Care Respir Med*. 26, 15083. doi:10.1038/npjpcrm.2015.83

10 van Dijk L, de Jong J, Westert G, de Bakker D. (2011) Variation in formulary adherence in general practice over time (2003–2007). *Fam Pract*. 28, 624–31. doi:10.1093/fampra/cmr043

11 Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, *et al*. (2012) Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. *Ann Intern Med*. 3; 156(7), 512–24. doi:10.7326/0003-4819-156-7-201204030-00411

12 Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, *et al*. (2014) Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*.(4), CD008965. doi:10.1002/14651858.CD008965

13 Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R, *et al*. (2016) Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. *Health Technol Assess*. 20(42), 1–242. doi:10.3310/hta20420

14 Kaur Virk R, Gunalan V, Anantharajah Tambyah P. (2016) Influenza infection in human host: challenges in making a better influenza vaccine. *Expert Review of Anti-infective Therapy*.; doi:10.1586/14787210.2016.1155450 PMID: 26885890

15 Center for Disease Control and Prevention. Stopping the Spread of Germs at Home, Work & School. http://www.cdc.gov/flu/protect/stopgerms.htm. Accessed 4 March 2016

16 Public Health Agency of Canada. Vaccine coverage amongst adult Canadians: Results from the 2012 adult National Immunization Coverage (aNIC) survey. 2012. http://www.phac-aspc.gc.ca/im/nics-enva/vcac-cvac-eng.php. Accessed 4 March 2016

17 World Health Organization FaAOotUN. Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food. http://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf; Accessed 4 March 2016
18 Hao Q, Dong B, Wu T.(2015) Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev*. (2), CD006895. doi:10.1002/14651858.CD006895.pub3
19 Kang E-J, Kim SY, Hwang I-H, Ji Y-J. (2013) The effect of probiotics on prevention of common cold: a meta-analysis of randomized controlled trial studies. *Korean J Fam Med*. 34, 2–10. doi:10.4082/kjfm.2013.34.1.2
20 King S, Glanville J, Sanders M, Fitzgerald A, Varley D. (2014) Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis. *Br J Nutr*. 112(1), 41–54. doi:10.1017/S0007114514000075
21 Liu S, Hu PW, Du X, T Z, Pei X. (2013) *Lactobacillus rhamnosus* GG supplementation for preventing respiratory infections in children: a meta-analysis of randomized, placebo-controlled trials. *Indian J Pediatr*. 50, 377–81.
22 Ozen M, Kocabas S, Dinleyici E. (2015) Probiotics for the prevention of pediatric upper respiratory tract infections: a systematic review. *Expert Opin Biol Ther*. 15? 9–20. doi:10.1517/14712598.2015.980233
23 Sæterdal I, Underland V, Nilsen E. (2012) The effect of probiotics for preventing acute upper respiratory tract infection. *Glob Adv Health Med*. 1, 124–5. doi:10.7453/gahmj.2012.1.2.014
24 Vouloumanou E, Makris G, Karageorgopoulos D, Falagas M. (2009) Probiotics for the prevention of respiratory tract infections: a systematic review. *Int J Antimicrob Agents* 34(197), e1–e10.
25 Lenoir-Wijnkoop I, Gerlier L, Bresson J, Le Pen C, Berdeaux G. (2015) Public health and budget impact of probiotics on common respiratory tract infections: a modelling study. *PLoS One* 10: doi:10.1371/journal.pone.0122765
26 Public Health Agency of Canada. FluWatch—Public Health Agency of Canada. http://dsolsmed.phac-aspc.gc.ca/dsol-smed/fluwatch/fluwatch.phtml?lang=e. Accessed 4 March 2016
27 Statistics Canada. Population by sex and age group. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo10a-eng.htm. Accessed 4 March 2016
28 Government of Canada. Weekly Influenza Reports. http://healthycanadians.gc.ca/diseases-conditions-maladies-affections/disease-maladie/flu-grippe/surveillance/fluwatch-reports-rapports-surveillance-influenza-eng.php. Accessed 4 March 2016
29 Public Health Agency of Canada. About FluWatch. http://www.phacaspc.gc.ca/fluwatch/indexA-eng.php. Accessed 4 March 2016
30 Statistics Canada. Contact with a medical doctor, by age group and sex. Available at: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health115a-eng.htm. Accessed 4 March 2016
31 Kwong J, Stukel T, Lim J, McGeer A, Upshur R, Johansen H*, et al*. (2008) The effect of universal influenza immunization on mortality and health care use. *PLoS Med.* 5(10), e211. doi:10.1371/journal.pmed.0050211
32 Ispos Reid. BioAccess Commercialization Centre Canadian Baseline Survey. http://www.agwest.sk.ca/kaizen/BlogDocuments/BioAccess_CanadianBaselineSurvey.pdf. Accessed March 2016
33 Readers prefer probiotic pills to probiotic yogurt. (2011) *Consum Rep*. 76(11), 12.
34 FamilyHealthOnLine. http://www.familyhealthonline.ca/fho/familymedicine/FM_CostOfDoctorVisit_FHb13.asp. Accessed 4 March 2016
35 Well.ca. https://well.ca/products/ibuprofen-200-mg_203.html; Accessed 4 March 2016

36 Kwong J, Maaten S, Upshur R, Patrick D, Marra F. (2009) The effect of universal influenza immunization on antibiotic prescriptions: an ecological study. *Clin Infect Dis*. 49(5), 750–6. doi:10.1086/605087

37 Morgan S, Smolina K, Mooney D, Raymond C, Bowen M, Gorczynski C, *et al*. The Canadian Rx atlas, 3rd edition. https://openlibraryubcca/cIRcle/collections/ubccommunityandpartnerspublicati/47136/items/10048514. Accessed 4 March 2016

38 Palmer L, Rousculp M, Johnston S, Mahadevia P, Nicho lK. (2010) Effect of influenza-like illness and other wintertime respiratory illnesses on worker productivity: The child and household influenza-illness and employee function (CHIEF) study. *Vaccine* 28(31), 5049-56. doi:10.1016/j.vaccine.2010.05.011

39 Benseñor IM, Cook N, Lee I, Chown M, Hennekens C, Buring J, *et al*. (2001) Active and passive smoking and risk of colds in women. *Ann Epidemiol*. 11(4), 225–31.

40 Statistics Canada. Smokers by sex, provinces and territories. http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/health74b-eng.htm. Accessed 4 March 2016

41 Statistics Canada. Health indicator profile, annual estimates, by age group and sex, Canada, provinces, territories, health regions (2013 boundaries) and peer groups. http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=1050501—F32 Accessed 4 March 2016

42 Louhiala P, Jaakkola N, Ruotsalainen R, Jaakkola J. (1995) Form of day care and respiratory infections among Finnish children. *Am J Public Health* 85(8 Pt 1), 1109–12.

43 Jaakkola J, Heinonen O. (1995) Shared office space and the risk of the common cold. *Eur J Epidemiol*. 11(2), 213–6.

44 Jefferson T, Di Pietrantonj C, Rivetti A, Bawazeer G, Al-Ansary L, Ferroni E. (2014) Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev*. (3).

45 Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. (2012) Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev*. (8).

46 Public Health Agency of Canada (PHAC). Statement on Seasonal Influenza Vaccine for 2015–2016. http://www.phac-aspc.gc.ca/naci-ccni/flu-2015-grippe-eng.php—i. Accessed 4 March 2016

47 Gionet L. (2015) Flu Vaccination Rates in Canada. http://www.statcan.gc.ca/pub/82-624-x/2015001/article/14218-eng.pdf Accessed 4 March 2016

48 Monto A. (1994) Studies of the community and family: acute respiratory illness and infection. *Epidemiol Rev*. 16(2), 351–73

49 Lenoir-Wijnkoop I, Dapoigny M, Dubois D, van Ganse E, Gutiérrez-Ibarluzea I, Hutton J, *et al*. (2011) Nutrition economics–characterising the economic and health impact of nutrition. *Br J Nutr*. 105 (1), 157–66. doi:10.1017/S0007114510003041

50 Freijer K, Lenoir-Wijnkoop I, Russell C, Koopmanschap M, Kruizenga H, Lhachimi S, *et al*. (2015) The view of European experts regarding health economics for medical nutrition in disease-related malnutrition. *Eur J Clin Nutr.* 69(5), 539-45. doi:10.1038/ejcn.2014.280

51 Olsen R, Greisen G, Schrøder M, Brok J. (2016) Prophylactic Probiotics for PretermInfants: A Systematic Review and Meta-Analysis of Observational Studies. *Neonatology* 109(2), 105–12. doi:10.1159/000441274 PMID: 26624488

52 Ritchie M, Romanuk T. (2012) A meta-analysis of probiotic efficacy for gastrointestinal diseases. *PLoS One* 7(4), e34938. doi:10.1371/journal.pone.0034938

53 Sun J, Buys N. (2015) Effects of probiotics consumption on lowering lipids and CVD risk factors: a systematic review and meta-analysis of randomized controlled trials. *Ann Med*. 47(6):430–40. doi :10.3109/07853890.2015.1071872 PMID: 26340330

54 Grin P, Kowalewska P, Alhazzan W, Fox-Robichaud A. (2013) Lactobacillus for preventing recurrent urinary tract infections in women: meta-analysis. *Can J Urol.* 20(1):6607–14. PMID: 23433130

55 Lenoir-Wijnkoop I, Nuijten M, Gutiérrez-Ibarluzea I, Hutton J, Poley M, Segal L, *et al*. (2012) Concepts and methods in the economics of nutrition–gateways to better economic evaluation of nutrition interventions. *Br J Nutr*. 108(9), 1714-20. doi:10.1017/S0007114512003704. m

56 Canada Life. Working Environment Makes Maintaining Health and Wellbeing a Struggle. http://www.canadalife.co.uk/media/47471/perfectofficepressrelease.pdf. Accessed 29 March 2016

57 Caffarelli C, Cardinale F, Povesi-Dascola C, Dodi I, Mastrorilli V, Ricci G. (2015) Use of probiotics in pediatric infectious diseases. *Expert Rev Anti Infect Ther*. 13(12), 1517-35. doi:10.1586/14787210.2015.1096775

58 Wang Y, Li X, Ge T, Xiao Y, Liao Y, Cui Y, *et al*. (2016) Probiotics for prevention and treatment of respiratory tract infections in children: A systematic review and meta-analysis of randomized controlled trials. *Medicine* (Baltimore) 95(31), e4509. doi:10.1097/MD.0000000000004509

59 Ozen M, Kocabas Sandal G, Dinleyici EC. (2015) Probiotics for the prevention of pediatric upper respiratory tract infections: a systematic review. *Expert Opin Biol Ther*. 15(1), 9–20. doi:10.1517/14712598.2015.980233

60 Ioannidis JP. (2016) We need more randomized trials in nutrition-preferably large, long-term, and with negative results. *Am J Clin Nutr*. 103(6), 1385–6. doi: 10.3945/ajcn.116.136085

61 Maki KC, Slavin JL, Rains TM, Kris-Etherton PM. (2014) Limitations of observational evidence: implications for evidence-based dietary recommendations. *Adv Nutr*. 5(1), 7–15. doi:10.3945/an.113.004929

62 Centers for Disease Control and Prevention (CDC). FastStats—Physician office visits. www.cdc.gov/nchs/fastats/physician-visits.htm.

Chapter 9.3

Probiotics reduce health care cost and societal impact of flu-like respiratory tract infections in the USA: an economic modeling study

Irene Lenoir-Wijnkoop, Dan Merenstein, Daria Korchagina, Christa Broholm, Mary Ellen Sanders, Dan Tancredi

Published in: Front Pharmacol. 2019;10, 980

ABSTRACT

Acute respiratory tract infections (RTIs) of viral origin place a substantial burden on health care resources and society. Randomized controlled trials have shown positive effects of probiotics on clinical outcomes in these commonly occurring RTIs. Two meta-analyses published by the York Health Economics Consortium (YHEC) and Cochrane reported the efficacy of probiotics in reducing incidence and duration of RTIs, number of antibiotic courses, and days absent from work. The aim of this study was to assess the potential health-economic impact of probiotics on RTI-associated events and expenses in the US primary care setting. A state-transition microsimulation model reproduced a study population representative of the US national demographics for age and gender (1/1,000 sample). RTI incidence was based on the influenza-like illness outpatient consultation rate reported by the Centers for Disease Control and Prevention (CDC) FluView. Data on vaccination, on factors that negatively impact RTI outcomes, on resource utilization, and on productivity loss were obtained from US national databases. Analyses were performed for both meta-analyses independently. Outcomes included cost savings for the health care payer, related to a reduced number of RTI episodes, less outpatient consultations, and decreased medical prescriptions as well as cost savings from a broader societal perspective related to productivity loss. The analysis showed that generalized probiotic intake in the US population for 2017–2018 would have allowed cost savings for the health care payer of 4.6 million USD based on the YHEC scenario and 373 million USD for the Cochrane scenario, by averting 19 million and 54.5 million RTI sick days, respectively, compared to no probiotics. Antibiotic prescriptions decreased with 1.39–2.16 million courses, whereas absence from work decreased by 3.58–4.2 million days when applying the YHEC and Cochrane data, respectively. When productivity loss is included, total savings for society represented 784 million or 1.4 billion USD for the YHEC and Cochrane scenarios, respectively. Subgroup analyses demonstrated an incremental benefit of probiotics in at-risk groups, which might be of relevance for targeted interventions. Sensitivity analyses confirmed the robustness of the model outcomes. Our analysis demonstrated a positive impact of probiotics on the health care and economic burden of flu-like RTIs. Improved disease outcomes translated into considerable cost savings for both the payer and society.

INTRODUCTION

Acute respiratory tract infection (RTI) is a frequent illness, generally of viral origin. Clinical conditions range from mild cold symptoms to influenza, the most serious form of common acute RTI. In most health care settings, diagnostic tests that would differentiate between influenza and other forms of viral RTIs are not routinely performed. Although most acute RTI episodes resolve spontaneously,[1] RTIs result in a high number of outpatient consultations and pose a heavy burden on society and health care systems. Strategies to reduce the incidence and effects of common acute RTIs attract major public health interest, given the large number of individuals affected each year as well as the impact on patient health outcomes and on medical and personal costs. In order to facilitate disease monitoring, this overlapping group of acute viral respiratory infections is generally referred to as influenza-like illness (ILI).[2] Recently, the WHO defined ILI as "an acute respiratory illness with a measured temperature of >38°C and cough, with [symptom] onset within the past 10 days".[3] In the USA, information on outpatient visits to health care providers for ILI is collected through the US Outpatient Influenza-like Illness Surveillance Network.[4] For this system, ILI is defined as having a fever (>100°F or >37.8°C) and cough and/or sore throat (in the absence of a known cause).

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[5] Interest in the potential impact of probiotics on health outcomes has been increasing in recent years. This impact has been investigated in several therapeutic areas, including RTIs. According to a recent survey among health care providers who routinely prescribe medication, 61% had recommended probiotic food or supplements to their patients.[6] Several clinical studies have evaluated the effectiveness of probiotics when administered to healthy subjects in reducing the incidence and duration of infectious respiratory conditions.[7-9] Two large meta-analyses have investigated the preventative effect of taking probiotics *vs*. placebo. The York Health Economics Consortium (YHEC) performed a systematic review and meta-analysis on the duration of illness in healthy children and adults who developed acute respiratory infectious conditions;[10] results showed that probiotics significantly reduced RTI episode duration. The Cochrane Collaboration assessed the effectiveness of probiotics, compared with placebo, in the prevention of acute upper RTIs in healthy people of all ages and reported that probiotics reduced RTI incidence and antibiotic prescription rate.[11]

OBJECTIVES

Based on the above-mentioned meta-analyses reporting the positive outcomes of probiotics in RTI, we hypothesized that generalized use of probiotics would meaningfully reduce RTI duration and/or frequency and thus the use of health care resources and related expenses for RTI in the USA. The objective of this study was to quantify the effect of probiotics on RTI-related health and cost outcomes in the US primary care setting. The analysis also explored the effect of probiotic intake on productivity loss.

METHODS

Model Description

Our economic analysis compared generalized probiotic intake *vs*. no probiotic intake. We used a state-transition microsimulation model, which enabled us to track the disease pathway of each subject, accumulating costs and events dependent on individual baseline and/or time-varying characteristics. Two previously published economic evaluations of probiotics in RTIs inspired the model structure.[12,13] The study cohort was a representative sample of the US population in terms of demographics and known RTI-related risk factors. Model convergence was tested in order to ensure that the number of individuals in the analysis was sufficient to obtain robust results. The model comprised two health states, "at risk" and "ongoing RTI" (Figure 1).

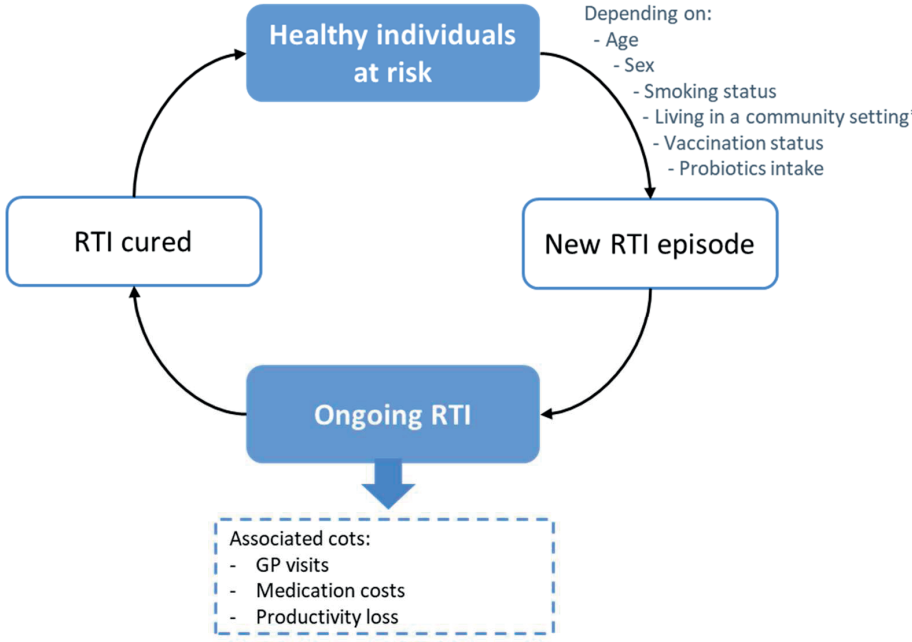
All individuals in the cohort were evaluated under each of the two probiotic intake regimens, generalized probiotic use *vs*. no probiotic use. For the analysis of each regimen, each subject started in the "at-risk" state and could move to "ongoing RTI" according to predefined transition probabilities, calculated based on US epidemiology data. The cycle length was 1 day, and the time horizon was 1 year, reflecting the 2017–2018 influenza season of FluView data from the Centers for Disease Control and Prevention (CDC).

Model Inputs and Data Sources

Probiotic Effect

The clinical effects of probiotics were obtained from the meta-analyses published by the YHEC and Cochrane.[10,11] These were used to conduct two independent scenario analyses comparing generalized probiotic use *vs*. non-use, each based on different assumptions: YHEC showed a significantly shorter duration of −0.77 days [−1.50 to −0.04] on an average duration of 7.4 days per episode of RTI, among otherwise healthy children and adults taking probiotics compared to those taking placebo. The Cochrane study reported that probiotics significantly reduced RTI duration by 1.89 days [1.75 to 2.03] per episode of an

Figure 1. Model structure



average duration of 8.82 days and RTI incidence by 30% (RR = 0.70 [0.50 to 0.84]) (Table 1). The authors also found a significant reduction of the antibiotic prescription rate of 35% (RR = 0.65 [0.45 to 0.94]), which was applied to both scenarios. Additionally, the YHEC meta-analysis studied the impact of probiotics on work absenteeism. The reported standardized mean difference (SMD) in the number of days absent from work was used to estimate the impact of probiotics on productivity loss. The Cochrane meta-analysis focused on unvaccinated individuals; therefore, no impact of probiotics sourced from the Cochrane meta-analysis was applied in vaccinated patients.

Demographic Structure of the Study Population

The demographic data by age and gender were obtained from the United States Census Bureau.[14]

Respiratory Tract Infection Incidence and Vaccination Status

The daily RTI incidence probabilities were estimated based on the ILI outpatient consultation rate as reported by CDC FluView.[15] The vaccination status of American citizens was taken into account in the base case to allow exclusion of a probiotic effect in vaccinated patients, as the Cochrane scenario excluded vaccinated subjects. That is, for a vaccinated patient, we specified that RTI incidence and duration were identical between the probiotic and no-probiotic scenarios, effectively excluding probiotic effects

Table 1. Summary over model inputs – epidemiological and resource utilization parameters

Model parameters				**Reference**
Influenza vaccination coverage				CDC FluVaxView 2018
Steps to ILI incidence estimation				
All cause consultations, all ages				NAMCS
Total ILI consultations, all ages				CDC FluView 2018
Clinical effect of probiotics				
YHEC	On RTI incidence: NA/On RTI duration: -0.77 days *vs.* placebo/On antibiotic use: NA, On work absenteeism: -0.17 SMD			King *et al*. 2014
Cochrane	On RTI incidence: RR=0.70* *vs.* placebo/On RTI duration: -1.89 days *vs*. placebo/On antibiotic use: RR=0.65 *vs*. placebo/On work absenteeism: NA			Hao *et al.* 2015
Risk factors				
Smoking				
Active smokers				CDC MMWR 2018
Passive smokers				National Cancer Institute 2017
Shared indoor environment				
School enrollment				United States Census Bureau 2018
Employment status				Bureau of Labor Statistics 2018
Living in a nursing home				Henry J Kaiser Family Foundation 2019
Impact of risk factors on RTI				
Smoking				
Active smokers	On RTI incidence: NA/ On RTI duration +16.8% *vs*. no smokers			Benseñor *et al*. 2001
Passive smokers	On RTI incidence: RR=1.15/ On RTI duration +4.5% *vs*. no smokers			Benseñor *et al.* 2001
Shared indoor environment				
Day care (including school) *vs*. home care	On RTI incidence: RR= 1.22/On RTI incidence: NA			Louhiala *et al.* 1995
Shared office *vs*. alone	On RTI incidence: RR= 1.07/On RTI incidence: NA			Jaakkola *et al*. 1995
Cost parameters				
Direct cost parameters	**% using the resource**	**Unit cost (by payer) (USD)**	**Copayment (USD)**	
PCP cost[#]	100%	74.16**	25**	Physician Fee Schedule
Antibiotics (Amoxillin)[§]	29%	6.49	0	Medi-span PriceRx 2018
Non-antibiotic medication	56.62%	26.59	11	Karve *et al.* 2013

Table 1. Summary over model inputs – epidemiological and resource utilization parameters (*continued*)

Model parameters				Reference
Indirect cost parameters	**% missing days**	**Number of missed days, mean (SD)**	**Cost per day lost (employer) (USD)†**	
Employee with ILI	42%	1.7 (5.1)	217.92	Palmer *et al*. 2010, Bureau of Labor Statistics 2018
Sick children with ILI	18%	0.5 (1.5)	217.92	Palmer *et al*. 2010, Bureau of Labor Statistics 2018

SMD standardized mean difference, NA not applicable, CDC, Centers for Disease Control and Prevention; ILI, influenza-like illness; NAMCS, National Ambulatory Medical Care Survey; YHEC, York Health Economics Consortium; RTI, respiratory tract infection; RR, risk ratio; MMWR, Morbidity and Mortality Weekly Report; PCP, primary care physician.
*Transformed from OR to RR using exact numbers and sample size.
**Reimbursed unit price of current procedural terminology code 99213.
#Published by the Centers for Medicare & Medicaid Services.
§Commonly used and recommended for by the CDC.
†Cost per absent day is based on daily wage from (Bureau of Labor Statistics, 2018).

for vaccinated patients. The prevalence of influenza vaccination in the USA was obtained from the CDC Fluvaxview.[16] The lower probability of getting ILI for vaccinated subjects was estimated based on the vaccination effect reported by two meta-analyses, for children and adults, respectively.[17,18]

Risk Factors

Several risk factors other than age are known to have an impact on RTI, such as smoking or a daily shared indoor environment. To guarantee stable and robust results, these risk factors were not part of the base case but were included in subgroup analyses that assessed the variability of the results across different subpopulations and identified subpopulations likely to benefit more from the use of probiotics.

Benseñor *et al*. carried out a randomized controlled trial (RCT) among 39,876 female participants to assess active and passive smoking in relation to frequency of colds.[19] The study showed no significant impact of active smoking on upper RTI incidence, while it significantly increased the risk of having a longer duration (RR >7 days) of 1.62 [1.40 to 1.87] for light smokers and 2.63 [2.02 to 3.44] for heavy smokers. In passive smokers, a higher RTI incidence [1.15 (1.05 to 1.26)] and a longer RTI duration per episode [4.5 (0.1 to 8.9)] were observed in comparison to non-smokers.

The CDC Morbidity and Mortality Weekly Report (MMWR) published the prevalence of active smoking among adults as well as among middle and high school students.[20,21] The prevalence of passive smoking was obtained from the National Cancer Institute.[22]

Daily shared indoor environments (*i.e.* children studying in school and adults working in a shared office) have been shown to increase the risk of acquiring an RTI, with an associated impact on RTI incidence.[1] Children in day care centers, aged 1–7 years, appeared to have a significantly higher risk of getting a respiratory infection than children staying at home [1.22 (1.13 to 1.31)].[23] In the model, this effect was also applied for children aged 8–15 years. The results of a study on adults working in a shared office environment showed a higher risk of having more than two cold episodes during a 12-month period [1.64 (1.08 to 2.50)].[24] Prevalence of shared indoor environments was based on school enrollment,[25] employment status,[26] and proportion of people living in a nursing home.[27]

Respiratory tract infection-related costs

Resource utilization consisted of estimated consultation fees for a primary care physician (PCP), cost of antibiotics and other prescribed medication resource use, and copayment.[28] Inpatient costs were not considered. Cost for consulting a PCP was taken from the Physician Fee Schedule[29] and based on the assumption of a single PCP consultation per RTI episode to align with the estimates of the RTI incidence derived from the number of ILI outpatient visits, collected through the US Outpatient Influenza-like Illness Surveillance Network.[4] The cost of antibiotics was based on a recent study that reported an antibiotic prescription during influenza seasons of 29%.[30] Due to the lack of data availability, prescribed medications other than antibiotics were included in this analysis as a single cost item, based on a publication that assessed health care costs associated with influenza.[31] The cost of over-the-counter medication among the general population was not included, as reliable information on cost estimates was insufficient.

A broader societal perspective was taken by combining the cost covered by insurance/copayment and ILI-related productivity losses.[32] An overview of all data inputs and sources is presented in Table 1.

Statistical analyses

The model was used to quantify the impact of generalized probiotic use *vs*. no probiotic use on each of the following outcomes: number of ILI events, number of ILI days, number of antibiotic prescriptions, number of days missed from work, PCP visit costs, medication costs, and productivity loss. Subgroup analyses were conducted on age, vaccination status, smoking status (active and passive), and living or working in a shared indoor environment. Two additional scenario analyses were conducted: (1) comparing a population with generalized probiotic intake *vs*. a population with current probiotic intake in the USA and (2) considering an alternative data source for productivity loss in ILI patients.

Uncertainty around model results due to model assumptions was further explored in a one-way sensitivity analysis, which considered two key parameters: avoided RTI days and saved total societal cost with probiotic use *vs*. no probiotic use (Table 2). All statistical analyses were performed and produced in Microsoft Excel (2016), and the model was developed with the utilization of Visual Basic for Applications (VBA) in Excel.

Table 2. Sensitivity analyses: lower and upper bounds of variation for model parameters

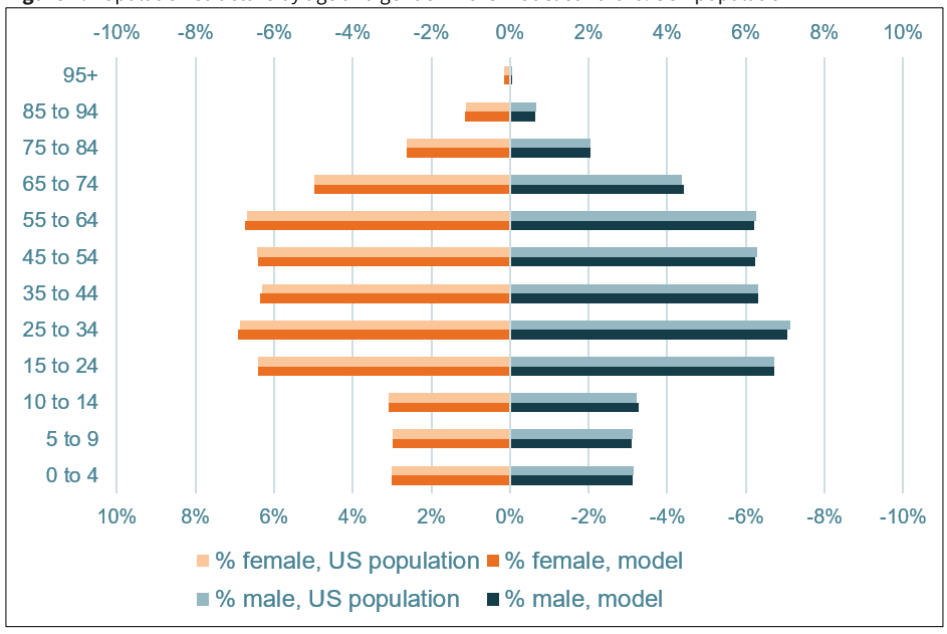
Parameter	Value			Source
	Base case	Lower	Upper	
YHEC Scenario (probiotic effects)				
Change duration per RTI episode	0.77	0.04	1.5	95% CI, King *et al.* 2014
Reduced antibiotic prescription (RR)*	0.65	0.45	0.94	95% CI, Hao *et al.* 2015
Change in loss of productivity, adults	0.87	0.153	1.581	95% CI, King *et al*. 2014 + assumption
Change in loss of productivity, children‡	0.26	0.045	0.465	
Cochrane Scenario (probiotic effects)				
Change in duration per RTI* episode	1.89	1.75	2.03	95% CI, Hao *et al*. 2015
Reduced incidence of RTI* (RR)	0.70	0.5	0.84	
Reduced antibiotic prescription* (RR)	0.65	0.45	0.94	
Change in loss of productivity, adults	0.87	0.153	1.581	95% CI, King *et al.* 2014 + assumption
Change in loss of productivity, children‡	0.26	0.045	0.465	
Both Scenarios				
Probability of non-antibiotic medication	56.62%	50.00%	60.00%	Assumption based on expert opinion
Antibiotic cost, 0-14 years	2.95	1.48	4.43	+/- 50% of base case value
Antibiotic cost, 15+ years	3.54	1.77	5.31	
PCP cost	99.16	69.64	124.44	Codes 99212 and 99214, Physician Fee Schedule

Upper and lower limits represent 95% confidence interval as reported by the indicated source *applied in non-vaccinated individuals only, ‡ productivity loss caused by sick child, PCP primary care physician, RR risk ratio, RTI respiratory tract infection

Model validity

A cohort of 329,256 individuals was generated based on the chosen sample rate. The model demonstrated a high precision in simulating the US population structure by age and gender (Figure 2). High accuracy was also achieved in simulating risk factor prevalence as well as ILI event incidence with <0.2% difference in total number of RTI events when compared to the FluView data. To ensure that the model provides robust results with a chosen sample size, convergence testing was conducted and confirmed the stability of estimates for both the YHEC and the Cochrane scenarios.

Figure 2. Population structure by age and gender in the model cohort *vs*. USA population



RESULTS

In the YHEC scenario, the base case analysis showed that the shorter duration of disease associated with probiotic intake engendered 19,012 fewer acute RTI days compared to no probiotics, while 1,393 antibiotic courses (−19.4%) were avoided in the evaluated study cohort (Table 3). As the YHEC meta-analysis did not investigate the effect of probiotics on RTI incidence, the difference in the number of RTI episodes and related physician consultations was not part of the base case analysis. When these outcomes are projected to the actual US population, this translates to potential cost savings associated with probiotic use of 4.6 million USD for the health care payer. When productivity loss related to absence from work is included, probiotic intake has the potential for additional total cost savings of 784 million USD for the USA.

Table 3. York Health Economics Consortium (YHEC) scenario: impact of probiotics on RTI-related events *vs*. no probiotics (sample size 1/1,000)

Event outcome	Probiotics	No probiotics	Difference	Difference in %
RTI days	163,701	182,713	-19,012	-10.41%
No. of antibiotic courses	5,804	7,197	-1,393	-19.36%
No. of missed work days	3,397	6,973	-3,576	-51.29%

In the Cochrane scenario, the base case analysis of the effect of probiotics on both a reduced RTI incidence and a shorter disease duration demonstrated a decrease of 4,103 RTI episodes, a reduction of 54,491 RTI days, and 2,166 antibiotics courses averted in the probiotic arm compared to the arm without probiotics (Table 4). Projection of the base case outcomes to the US population showed that probiotic use would result in cost savings of 373 million USD for the health care payer. For this scenario, when generalized probiotic use vs. no probiotic use are compared, the total decrease in RTI-associated expenses due to medical resource utilization and productivity loss combined equaled 1.4 billion USD.

Table 4. Cochrane scenario: impact of probiotics on RTI-related events *vs*. no probiotics (sample size 1/1,000)

Event outcome	Probiotics	No probiotics	Difference	Difference in %
RTI episodes	20,568	24,671	-4,103	-16.63%
RTI days	163,107	217,598	-54,491	-25.04%
No. of antibiotic courses	5,026	7,192	-2,166	-30.12%
No. of missed work days	2,753	6,971	-4,217	-60.50%

Subgroup analyses of risk factors showed that an incremental benefit of probiotics was observed in children aged ≤15 years, in individuals sharing a daily indoor environment, and in passive smokers. The positive impact of probiotics was highest in the pediatric population that constituted 19.8% of the cohort population, but in which probiotic use contributed to 41.3% of avoided RTI days and 26.3% of the total cost savings. Results of the unvaccinated subgroup analysis showed that the 53.7% of unvaccinated individuals in the model population contributed to 56% of avoided RTI days and 63.9% of saved total costs. The outcomes of the subgroup analyses are summarized in Table 5.

In the base case analysis, current probiotic intake was disregarded even though probiotic consumption would be expected to influence the reported RTI incidences and subsequently our study outcomes. Therefore, a scenario analysis was carried out based on estimated probiotic intake. According to the National Health Interview Survey (NHIS), 1.6% of American adults take probiotics and/or prebiotics as dietary supplements.[33] Further, it has been estimated that dietary supplements account for about 36% of the probiotic sales in the USA; the remaining 64% of the market represents thus probiotic foods.[34] Therefore, an overall 4.4% probiotic intake among the US population was used to include current probiotic consumption in a scenario analysis. This showed that outcomes were only slightly different from the base case, confirming the robustness of the model.

Table 5. Subgroup analysis by risk factors (age, smoking, and living in a shared daily environment) (sample size 1/1,000)

Subgroup	% of model population	% of avoided RTI days	% of total societal cost savings
YHEC Scenario			
Children (aged 0-15)	19,81%	41,30%	26,29%*
Passive smokers	26,59%	34,60%	30,03%
Individuals with shared indoor environments	53,19%	55,55%	71,88%
Unvaccinated individuals	53,70%	56,10%	63,87%
Cochrane Scenario			
Children (aged 0-15)	19,81%	34,35%	34,62%*
Active smokers	12,50%	11,93%	13,13%
Passive smokers	26,59%	34,11%	31,23%
Individuals with shared indoor environments	53,19%	58,25%	67,24%

DISCUSSION

We developed a state-transition microsimulation model to quantify the effect of probiotics on RTI-related health and cost outcomes in the USA. The analysis considered the impact of generalized probiotic intake from a health care payer's perspective in primary care, as well as in a broader societal setting by including productivity loss associated with flu-like RTI. The model accurately reproduced the US population structure, the incidence pattern, and the risk factor prevalence over the study period. Two meta-analyses reported clinical benefits of probiotics, one showing a reduction of disease duration and the other both a decrease of disease incidence and duration (Table 1). While the changes are small at an individual level, when applied to the US population, the health impact is sizable, ranging from an estimated 19,012,000 to 54,491,000 fewer RTI days, 1,393,000 to 2,166,000 averted antibiotic courses, and 3,576,000 to 4,217,000 avoided missed work days, according to the YHEC scenario and the Cochrane scenario, respectively. The Cochrane scenario showed a higher overall impact on public health, due to the fact that it considered both a shorter RTI duration and a reduced RTI incidence. In terms of cost savings, the impact of avoided RTI events, translated to the US population, represented a potential total amount of approximately 1.4 billion USD, of which 370 million USD represents savings for the health care payer.

When cross-validation is performed, the findings of this US analysis were consistent with the previously published French and Canadian assessments.[12,13] The proportion of avoided RTI days in the population with probiotics *vs*. no probiotics in the models was similar to the results in the current analysis for both the YHEC and Cochrane scenarios. Differences in other outcomes were to be expected due to country-specific

characteristics, related to vaccination coverage, prescription patterns, cost inputs, or different conditions in absence from work.

Strengths and limitations

In the present analysis, we accurately simulated the US general population structure, vaccination status and prevalence, and the ILI incidence pattern of the studied flu season. The incidence data represented only the proportion of PCP visits due to ILIs, which is known to be relatively low[35,36] and likely lead to an underestimation.

One of the base case scenarios only considered the effects of probiotics among the unvaccinated individuals, in line with the results of the Cochrane meta-analysis. The results of the model were therefore conservative, since probiotics can potentially have effects on the vaccinated individuals.[37,38] Another aspect of probiotic intake not captured in the model concerns the role probiotics may play in the reduction of antibiotic use.[39] The CDC estimates that of the 44% of outpatient antibiotics prescribed to treat patients with respiratory conditions, half are unneeded.[40] Reduced antibiotic use and the associated risk of antibiotic resistance may have considerable public health relevance as well as additional cost consequences.[41]

A limitation of our analysis is that probiotics were considered as a general category and not included in our assessment at the strain level. Different probiotic strains may have different effects on RTIs, but because our evaluation was based on two specific meta-analyses, we effectively included all relevant probiotic strains evaluated in one or more of the clinical trials that were pooled via these meta-analyses. Further, data available for probiotic use in the USA are not segregated based on specific strains. Advances have been made in unraveling the wide array of molecular mechanisms by which probiotic organisms can interact with host cells and on understanding how this might translate into a clinical effect.[42] Certain health benefits depend on core properties that are conserved among different probiotics, while other benefits appear to be more strain specific.[5,43] An expression of shared efficacy among many different strains may derive from common mechanisms among taxonomic groups that are at a higher order than a strain, such as species or genus. An example of such a shared mechanism is production of short-chain fatty acids. In the case of prevention of RTIs, the mechanism is not known, although it may likely involve probiotic interactions with the immune system. For purposes of this analysis, we consider it sufficient to note that studies included in the meta-analyses, upon which it is based, included interventions from a variety of different *Lactobacillus* and *Bifidobacterium* strains.

As in the previous French and Canadian analyses,[12,13] the cost of probiotics was not included as a factor in our model. Although costs of probiotic foods and dietary supplements do not weigh on the health care payers' resources, their purchase may put an extra burden on the average household expenses. Due to an absence of reliable information and a great variation in products with a wide range of unit prices, it was not possible to evaluate how much this would represent. However, these additional household costs would probably be offset by other expenses, such as costs related to self-medication and purchase of over-the-counter drugs[44] and costs related to informal care for sick children or the elderly[45] and associated with missed schooldays.[46,47]

CONCLUSION

The model demonstrated a positive impact of probiotic consumption on health outcomes in flu-like RTI and the associated patient burden by reducing the number of RTI episodes, the number of days patients spent with RTI symptoms, and the need for antibiotics. Improved patient outcomes translated into considerable cost savings for both the payer and society. These results suggest that recommending daily probiotic consumption may be justified for particular at-risk populations, such as children or individuals with a shared indoor environment, for which this study shows a higher incremental benefit. Such action should be in combination with a cost-effectiveness analysis of implementation to further define the extent to which probiotics contribute to reducing both health care spending and out-of-pocket costs for the management of flu-like infections.

REFERENCES

1 Dasaraju, PV, Liu C. (1996) "Infections of the Respiratory System," editor.Source Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; in *Medical Microbiology*. Dasaraju PV, Liu C. Editors In: Baron S

2 Fowlkes A, Giorgi A, Erdman D, Temte J, Goodin K, Di Lonardo, S, *et al.* (2014) Viruses associated with acute respiratory infections and influenza-like illness among outpatients from the Influenza Incidence Surveillance Project, 2010–2011. *J Infect Dis.* 209 (11), 1715–1725. doi:10.1093/infdis/jit806

3 Fitzner J, Qasmieh S, Mounts AW, Alexander B, Besselaar T, Briand S, *et al*. (2018) Revision of clinical case definitions: influenza-like illness and severe acute respiratory infection. *Bull World Health Organ*. 96 (2), 122–128. doi:10.2471/BLT.17.194514

4 CDC ILInet. (2018) Centers for Disease Control and Prevention. Weekly U.S. influenza surveillance report 2018. https://www.cdc.gov/flu/weekly/overview.htm

5 Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, *et al*. (2014) Expert consensus document: the International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat. Rev. Gastroenterol. Hepatol.* 11 (8), 506–514. doi:10.1038/nrgastro.2014.66

6 Draper K, Ley C, Parsonnet J. (2017) Probiotic guidelines and physician practice: a cross-sectional survey and overview of the literature. *Benef Microbes*. 8 (4), 507–519. doi:10.3920/BM2016.0146

7 de Vrese M., Winkler P, Rautenberg P, Harder T, Noah C, Laue C, *et al*. (2005) Effect of *Lactobacillus gasseri* PA 16/8, *Bifidobacterium longum* SP 07/3, *B. bifidum* MF 20/5 on common cold episodes: a double blind, randomized, controlled trial. *Clin. Nutr*. 24 (4), 481–491. doi:10.1016/j.clnu.2005.02.006

8 Leyer GJ, Li S, Mubasher ME, Reifer C, Ouwehand AC. (2009) Probiotic effects on cold and influenza-like symptom incidence and duration in children. *Pediatrics* 124 (2), e172–e179. doi:10.1542/peds.2008-2666

9 Berggren A, Lazou Ahrén I, Larsson N, Önning G. (2011) Randomised, double-blind and placebo-controlled study using new probiotic lactobacilli for strengthening the body immune defence against viral infections. *Eur J Nutr.* 50 (3), 203–210. doi:10.1007/s00394-010-0127-6

10 King S, Glanville J, Sanders ME, Fitzgerald A, Varley D. (2014) Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis. *Br J Nutr.* 112 (1). doi:10.1017/S0007114514000075

11 Hao Q, Dong BR, and Wu T. (2015) Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst. Rev.* 3 (2), CD006895. doi:10.1002/14651858.CD006895.pub3

12 Lenoir-Wijnkoop I, Gerlier L, Bresson JL, Le Pen C, Berdeaux G. (2015) Public health and budget impact of probiotics on common respiratory tract infections: a modelling study. *PLoS One* 10 (4), e0122765. doi:10.1371/ journal.pone.0122765

13 Lenoir-Wijnkoop, I, Gerlier L, Roy D, Reid G. (2016) The clinical and economic impact of probiotics consumption on respiratory tract infections: projections for Canada. *PLoS One* 11 (11), e0166232. doi:10.1371/journal. pone.0166232

14 United States Census Bureau. (2018) United States Census Bureau. Population by single year age groups 2018. https://www.census.gov/data-tools/demo/idb/region.php?N=Results&T=15&A=separate&RT=0&Y=201 8&R=-1&C=US.

15 CDC FluView. (2018). CDC FluView. National, regional, and state level outpatient illness and viral surveillance 2018. https://gis.cdc.gov/grasp/fluview/ fluportaldashboard.html.
16 CDC Fluvaxview. (2018). CDC vaccination coverage. https://www.cdc.gov/flu/fluvaxview/reportshtml/trends/index.html
17 Jefferson T, Rivetti A, Harnden A, Di Pietrantonj C, Demicheli V. (2008) Vaccines for preventing influenza in healthy children. *Cochrane Database Syst. Rev.* 16 (2), CD004879. doi:10.1002/14651858.CD004879.pub3
18 Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di Pietrantonj C. (2018) Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst. Rev*. (2), CD001269. doi:10.1002/14651858.CD001269.pub6
19 Benseñor IM, Cook NR, Lee IM, Chown MJ, Hennekens CH, Buring JE, *et al*. (2001) Active and passive smoking and risk of colds in women. *Ann. Epidemiol.* 11 (4), 225–231. doi:10.1016/S1047-2797(00)00214-3
20 Jamal A, Phillips E, Gentzke AS, *et al*. (2018) Current Cigarette Smoking Among Adults — United States, 2016. *MMWR Morb Mortal Wkly Rep* 67, 53–59. doi:http://dx.doi.org/10.15585/mmwr.mm6702a1
21 Wang TW, Gentzke A, Sharapova S, Cullen KA, Ambrose BK, Jamal A. (2018) Tobacco Product Use Among Middle and High School Students — United States, 2011–2017. *MMWR Morb Mortal Wkly Rep* 67, 629–633. doi:http://dx.doi.org/10.15585/mmwr.mm6722a3external icon
22 National Cancer Institute. (2017) National Cancer Institute. Secondhand smoke exposure. https://progressreport.cancer.gov/prevention/smoke_exposure
23 Louhiala PJ, Jaakkola N, Ruotsalainen R, Jaakkola JJK. (1995) Form of day care and respiratory infections among Finnish children. *Am J Public Health*. 85 (8 Pt 1), 1109–1112. doi:10.2105/AJPH.85.8_Pt_1.1109
24 Jaakkola JJK, Heinonen OP. (1995) Shared office space and the risk of the common cold. *Eur J Epidemiol*. 11 (2), 213–216. doi:10.1007/BF01719490
25 United States Census Bureau. School enrollment in the United States: October 2017—detailed tables. https://www.census.gov/data/tables/2017/demo/school-enrollment/2017-cps.html
26 United States Department of Labor. Bureau of Labor Statistics. Labor force statistics from the current population survey (2017 data) [cited 2018 December 19]. https://www.bls.gov/cps/cpsaat03.htm
27 Henry J Kaiser Family Foundation. Total number of residents in certified nursing facilities 2019. https:// www.kff.org/other/state-indicator/number-of-nursing-facility-residents/?currentTimeframe=0&sortModel=%7B%22colId%22:%22Location%22,%22sort% 22:%22asc%22%7D
28 Henry J Kaiser Family Foundation. Employer health benefits survey 2017. https://www.kff.org/report-section/ehbs-2017-section-9-prescription-drug-benefits/
29 Centers for Medicare & Medicaid Services. Physician fee schedule 2018. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/
30 Havers F P, Hicks LA, Chung JR, Gaglani M, Murthy K, Zimmerman RK, *et al*. (2018) Outpatient antibiotic prescribing for acute respiratory infections during influenza seasons. *JAMA Netw Open* 1(2), e180243. doi:10.1001/ jamanetworkopen.2018.0243
31 Karve S, Misurski DA, Meier G, Davis KL. (2013) Employer-incurred health care costs and productivity losses associated with influenza. *Hum Vaccin Immunother.* 9 (4), 841–857. doi:10.4161/hv.23413
32 Palmer LA, Rousculp MD, Johnston SS, Mahadevia PJ, Nichol KL. (2010) Effect of influenza-like illness and other wintertime respiratory illnesses on worker productivity: the Child and

Household Influenza-Illness and Employee Function (CHIEF) study. *Vaccine* 28 (31), 5049–5056. doi:10.1016/j.vaccine.2010.05.011

33 Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. (2015) Trends in the use of complementary health approaches among adults: United States, 2002–2012. *Nat. Health Stat. Report*. 10 (79), 1–16.

34 Vanderhoof JA, Young R. (2008). Probiotics in the United States. *Clin. Infect. Dis.* 46 Suppl 2, S67–S72; discussion S144–S151. doi:10.1086/523339

35 Biggerstaff M, Jhung MA, Reed C, Fry AM, Balluz L, Finelli L. (2014) Influenza-like illness, the time to seek healthcare, and influenza antiviral receipt during the 2010–2011 influenza season—United States. *J Infect Dis.* 210 (4), 535–544. doi:10.1093/infdis/jiu224

36 Peppa M, Edmunds WJ, Funk S. (2017) Disease severity determines health-seeking behaviour amongst individuals with influenza-like illness in an Internet-based cohort. *BMC Infect Dis.* 17 (1), 238. doi:10.1186/ s12879-017-2337-5

37 Yaqoob P. (2014). "Ageing, immunity and influenza: a role for probiotics?" *Proc Nutr Soc*. 73(2), 309-17. doi:10.1017/S0029665113003777

38 Zimmermann P, Curtis N. (2018) The influence of probiotics on vaccine responses—a systematic review. *Vaccine*. 36 (2), 207–213. doi:10.1016/j. vaccine.2017.08.069

39 King S, Tancredi D, Lenoir-Wijnkoop I, Gould K, Vann H, Connors G, *et al*. (2018) Does probiotic consumption reduce antibiotic utilization for common acute infections? A systematic review and meta-analysis. *Eur. J. Public Health*. 29 (3), 494–499. doi:10.1093/eurpub/cky185

40 CDC Newsroom. (2016). CDC: 1 in 3 antibiotic prescriptions unnecessary. https://www.cdc.gov/media/releases/2016/p0503-unnecessary-prescriptions.html

41 Michaelidis CI, Fine MJ, Lin CJ, Linder JA, Nowalk MP, Shields RK, *et al*. (2016) The hidden societal cost of antibiotic resistance per antibiotic prescribed in the United States: an exploratory analysis. *BMC Infect Dis.* 16 (1), 655. doi:10.1186/s12879-016-1990-4

42 Kleerebezem M, Binda S, Bron PA, Gross G, Hill C, van Hylckama Vlieg JE, *et al*. (2019) Understanding mode of action can drive the translational pipeline towards more reliable health benefits for probiotics. *Curr Opin Biotechnol.* 56, 55–60. doi:10.1016/j.copbio.2018.09.007

43 Sanders ME, Benson A, Lebeer S, Merenstein DJ, Klaenhammer TR. (2018) Shared mechanisms among probiotic taxa: implications for general probiotic claims. *Curr Opin Biotechnol*. 49, 207–216. doi:10.1016/j. copbio.2017.09.007

44 Klepser ME. (2014) Socioeconomic impact of seasonal (epidemic) influenza and the role of over-the-counter medicines. *Drugs* 74 (13), 1467–1479. doi:10.1007/s40265-014-0245-1

45 Chari AV, Engberg J, Ray KN, Mehrotra A. (2015) The opportunity costs of informal elder-care in the United States: new estimates from the American time use survey. *Health Serv Res*. 50 (3), 871–882. doi:10.1111/1475-6773.12238

46 Chari AV, Engberg J, Ray KN, Mehrotra A. (2015) The opportunity costs of informal elder-care in the United States: new estimates from the American time use survey. *Health Serv Res*. 50 (3), 871–882. doi: 10.1111/1475-6773.12238

47 NCCID. (2014). Is school closure an effective strategy to control influenza? https://nccid.ca/wp-content/uploads/sites/2/2015/03/SCHOOLS_Factsheet_ENGLISH_pdf

Chapter 10

Ten years of nutrition economics - retrospect and prospects

BACKGROUND

Our daily food is important for health. Adequate nutrition is a *sine qua non* for the harmonious development of each human being. Until the beginning of the twentieth century nutritional deficiency diseases due to an insufficient intake of micronutrients occurred frequently, leading to impaired physiological and cognitive functioning and even irreversible pathologies.[1,2] The discovery that these diseases were the consequence of a lack of vitamins and essential minerals, provided new insights on the role of food constituents to successfully treat and prevent such illnesses. This new understanding about the vital impact of dietary inadequacies and their far-reaching negative effects on health triggered an unequalled interest in nutrition science. It marked the beginning of the development of adapted nutrition strategies. Measures of food supplementation were established during the world wars, the first food recommendations were established, food fortification programs for the general population were developed.[3-5] As a consequence, a steady rapprochement between the science of nutrition and the field of medical care occurred. The surge of degenerative and civilization diseases that accompanied the demographic and epidemiological transitions of the second part of last century further tightened the link between nutrition and medicine. In order to build a reliable evidence-base for substantiated nutrition guidance, claim-approvals and targeted population-oriented interventions, biomedical scientists and other interested parties started to conduct nutritional investigations using clinical trials. These efforts, in line with the current standards of good clinical practices turned out to be costly, time-consuming and sometimes even with inconclusive outcomes.[6] In 2011 this situation inspired the creation of Nutrition Economics, a new discipline at the intersection of nutrition, medicine and (health) economics, defined as "*The discipline dedicated to researching and characterizing health and economic outcomes in nutrition for the benefit of society*".

ONE DECADE OF NUTRITION ECONOMICS

Shortly after the first expert consensus on nutrition economics,[7] a review was undertaken to identify existing research characterizing health and economic outcomes in nutrition. The selected publications concerned human studies reporting a measurable change in costs associated with changes in health status due to a nutrition intervention and relevant to the socio-economic environment. Records that reported the economic evaluation of medical nutrition do not reflect a food pattern or change in diet and were excluded. The outcomes of this review could be divided in three sections: economic studies of micronutrient deficiencies and malnutrition; economic studies of

dietary improvements; economic studies of functional foods. The analysis confirmed that nutrition can have a powerful impact on the health and the economic situation of societies; that the approaches and methodologies used were *ad hoc* in nature and widely varied in quality; and that there was a lack of implementation of many of the cost-effective nutrition interventions.[8]

At that moment in time, literature searches based on the use of a simple subject research with the term "nutrition economics" did not score one single hit in a dozen of consulted biomedical and economic databases, even when leaving out the double quotation marks. At the end of 2021, the Medline entry "nutrition economics" yielded a total result of 548 references over the timeframe 1945-2021, thus revealing that nutrition economics had been indexed as a new qualifier in the MeSH entry combinations. This confirms that the concept has been acknowledged as a rising research field since the initial proposal of nutrition economics, ten years ago.

A more detailed look at the retrieved references shows that a total of seven documents prior to the seventies primarily deal with food allocation programs and quality of nutrition related to food expenditures. Studies published since the seventies pertain to medical nutrition for over 80%, including the period 2012-2021 (n=157, with exclusion of evaluations of procedures and tube devices). This predominance of health economic studies on nutritional support in patients rather than on the impact of daily food products in the general population can be explained by the many challenges of nutrition evaluations, related to the difficulty to establish a causal link between consumption of a food product and an individual's future health status even when excluding the many uncontrollable confounding factors in the real-world setting.[9]

Medical nutrition refers to both parenteral nutrition regulated by legislation that is very close to pharma, and all forms of enteral nutrition, *i.e*. nutritional products ingested orally or via tube feeding into the digestive tract, regulated under food legislation.[10,11] Regulatory bodies require that medical nutrition is dispensed under supervision of a medical professional.[12,13] Their utilization in the delineated setting of a health care structure allows to monitor and quantify the cost-effectiveness of a nutritional intervention (e.g. reductions in mortality, in complication rates, drug administration, length-of-stay and in the proportion of patients readmitted to hospital) under good controlled circumstances compared to a community environment with its array of confounders.[14] This is one of the reasons why most of the published literature is dedicated to health economic evaluations of medical nutrition in target groups of patients who are hospitalized or staying in a specific institution, rather than being performed in free-living healthy (at-risk) individuals.

A second reason for the high proportion of nutrition economic assessments on medical nutrition can be sought in the active role third-party payers play in the process of health care provisions. In clinical practice they represent a clearly identified stakeholder and their involvement is key in the decisions/management of reimbursement of health care expenses, medical therapies, pharmaceuticals and other means for treating diseases conditions. A determining factor in these cost-sharing arrangements is the balance between benefits and harms *vs*. the cost of an intervention. Prescription of medical nutrition thus becomes more or less contingent on the results of well-conducted clinical trials, mostly funded and/or co-performed by the manufacturer who has (business) interest and the possibility to demonstrate the added value of his brands through measurable well-monitored endpoints over a relatively short timespan. This drastically differentiates the circumstances of health economic assessments conducted for medical nutrition and food-for special-medical-purposes from evaluations of the health impact of food purchased by consumers based on multifactorial individual choices and paid out-of-the-pocket without involvement of nutrition professionals or third-party payers. In the absence of engaged third-party payers, the number of stakeholders willing and capable to bear the expenses of meaningful cost-effectiveness studies of nutritional interventions remains limited. The demonstration of beneficial effects that often consist of health maintenance or delayed disease onset on the long term, is complex and far less profitable to private firms than investing in advertisement and marketing campaigns.

Two additional issues hampering meaningful nutrition economic evaluations in the general population are 1) the paucity of data from prospective studies on staple food or mass brands and 2) the difficulty to monitor health conditions over long periods of time. The first point can be obviated by the use of various existing data sources, like meta-analyses, published literature, databases, clinical trials, epidemiological observations, and Delphi panels. The second issue can be addressed through modelling techniques that allow to extrapolate the available short-term evidence over time in order to quantify outcomes beyond the study period or to link intermediate endpoints to final outcomes.[15] These modelling methods are considered to constitute an adequate approach for estimating long-term health- and financial consequences of public health programs and a valuable contribution in evidence-informed decision making.

Lastly, without the support that is usually provided in case of a dietary prescription or for adhering to a specific food intake, it is important to limit the eventuality that individuals participating in a community-based study setting fail to engage in the 'intervention'. In a perspective of broad public health measures, the robustness of nutrition economic data analyses should be ensured. As discussed in chapter 4, at the introduction of the nutrition economics concept, newborns at risk of atopic dermatitis fed with infant

formula provided a good option for the proof-of-concept. The study population is easy to follow because of standard regular medical surveillance and not prone to unhealthy food craving. Since the publication of this proof-of-concept study, similar economic evaluations have been reported, not only on atopic dermatitis,[16] but increasingly also on cow's milk allergy[17,18] and on feeding modalities in low-birth-weight infants.[19] Finally, the infant population can also be useful for studying another health concern frequently encountered by young parents: excessive baby crying as the expression of functional gastrointestinal disorders. Although these disorders are considered benign, they lead to repeated medical consultations and thus represent a burden for healthcare facilities as for the family budget and wellbeing.[20] The related expenses have been calculated and show the relevance of implementing strategies including appropriate nutritional recommendations to diminish the use of costly remedies and treatments lacking in evidence of effectiveness.[21,22]

Of course, modelling studies for nutrition economic assessments are not limited to babies. Identifiable at-risk subjects can be found among all age groups of the general public in spite of a high variety in food patterns; and reliable evidence can originate from national registries, formularies, health economic databases, institutes of statistics and food consumption surveys. For instance, at the other end of the age spectrum, reduced bone mass is a real public health concern. There is long-standing insight about the relationship between calcium intake, the level of vitamin D in the body and bone health.[23] However, before introducing the concept of nutrition economics, health economic analyses mainly focused on the healthcare burden and cost-benefits associated with clinical and pharmaceutical/hormonal management of fractures[24,25] and in a later stage on screening strategies and quality of life impact.[26,27] Preventive strategies based on daily nutritional approaches were not taken into account. After publication of the study discussed in chapter 6, a series of similar analyses on dairy products followed.[28] Currently, medical specialists and primary care practitioners still privilege pharmaceutical supplements for limiting bone demineralization, even though a lack of compliance from the patients is well known and documented.[29] Nevertheless, a tendency to better exploit the potential health value of common and affordable food products in the prevention of osteoporosis and osteoporotic fractures seems to be emerging. Indeed, an editorial published in 2018 ended with the conclusion that "*the current scientific evidence suggests that the use of dairy products to prevent bone fractures is an economically beneficial intervention, and promoting the use of dairy products needs to be reinforced*".[30] Hence, beyond the selection of a targeted population-group for conducting nutrition economic analyses , a distinct class of food offers an alternative option for evaluating the influence of improved daily diets on health care costs and -savings. This has been illustrated for dairy products

in indications other than osteoporosis, as discussed in chapter 8 and also shown in a number of common conditions in the general population.[31-33]

Another food category to which nutrition economic modelling has been applied over the last ten years are probiotics. There is a considerable amount of evidence regarding the positive effects of probiotics in the prevention or alleviation of diarrhea, a phenomenon many people are experiencing, in particular when receiving an antibiotic treatment.[34,35] This effect is accompanied by a reduced healthcare burden and cost-savings as shown in the hospital setting where the health economic evaluation of antibiotic associated diarrhea can build on clinically controlled data.[36]

With regard to the cost-saving potential of probiotics in non-intestinal health concerns, such as common respiratory infections and flu-like illness, within this retrospective it is worth mentioning a recent publication from a collaborator of the U.S. Army Research Institute of Environmental Medicine, who refers to the work presented in chapter 9c of this thesis as an option of interest for the cost-efficient reduction of the burden of respiratory tract infections, particularly in high-risk groups of unvaccinated individuals and those sharing indoor environments (e.g., military barracks).[37]

Lastly, pulses and fibers form a third common food group for which the nutrition economic effects in the general population have now been studied. The related analyses aim to estimate and predict avoidable health care cost and potential savings from a society perspective including impact on productivity, related to various frequently occurring diseases like type 2 diabetes, cardiovascular diseases and colorectal cancer.[38-40]

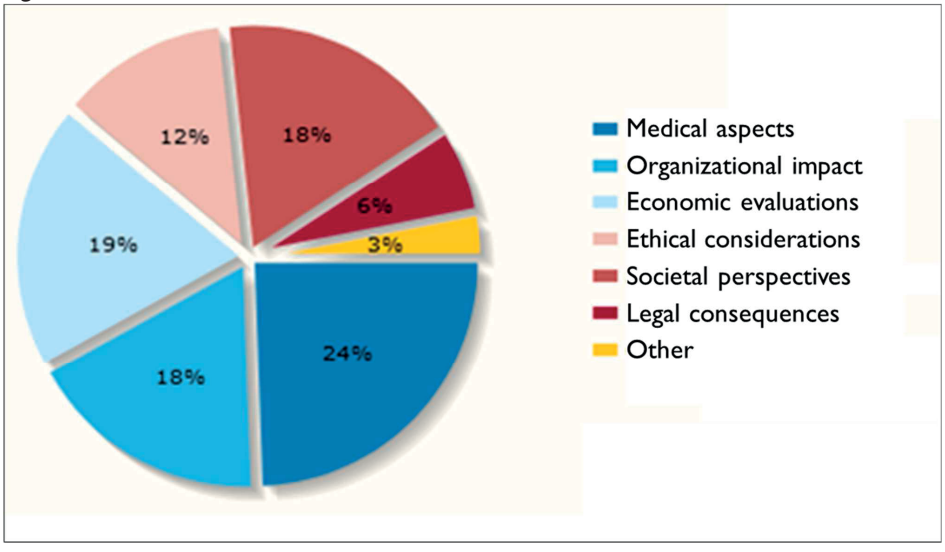
As in the case of medical nutrition, many of the published nutrition economic studies have been made possible by grants, unrestricted or not, from companies or food federations. It cannot be excluded that the willingness-to-pay of these funders is inspired by a business interest based on the expectancy to leverage demonstrated beneficial results as convincing arguments for health policymakers in charge of establishing and implementing food guidance for the general population. It does not really matter whether those studies are paid on private or public funds as long as the independency of the research protocol, execution modalities and outcomes reporting is warranted. Results from reliable nutrition interventions, both in clinical practice and in a community setting, are urgently needed to improve evidence-informed healthy food strategies and dietary recommendation guidance.

Theoretically, prevention and health promotion are not less important than cure and care. In practice however, on average only 3% of the healthcare budget is devoted

to prevention and health promotion.[41,42] This extremely low rate of investment was confirmed by a recent survey covering health technology assessment (HTA) agencies, public administrations, and other health economic agencies worldwide. HTA is defined as: a multidisciplinary process that uses explicit methods to determine the value of a health technology, a health technology being any intervention developed to prevent, diagnose or treat medical conditions; promote health; provide rehabilitation; or organize healthcare delivery.[43,44] In 2014 the HTAi society formally recognized nutrition as a health technology, an important milestone in the first years of nutrition economics.

The above-mentioned survey showed that the evaluation of public health interventions remains a neglected area (Figure 1).[45] In addition, more than half of the reported public health interventions focus on secondary and tertiary prevention, while among the primary intervention candidates screening and vaccination represent by far the largest assessment-items.

Figure 1. Evaluation of Public Health interventions



Other: environmental aspects, cost-benefit analysis, participation and collection of experiential and contextual data

Less than 2% of the evaluated public health interventions had a direct link with nutrient intake (water fluoridation, price regulations on health affecting consumption of sugars and vegetables). One of the limitations of this survey was its distribution via the HTA channels only, thereby overlooking assessments and feedback from public health nutrition specialists in academia and other scientific research institutes. These appear to be more and more engaged in a variety of assessments related with

national food recommendations and dietary guidelines,[46,47] educational programs,[48,49] health policies,[50,51] food delivery systems,[52,53] the affordability of nutritionally balanced diets.[54,55] The list of references is impressive, even without considering areas that are closely intertwined with the economic evaluation of nutrition intervention programs as part of health promotion policies, *i.e* behavioural and lifestyle economics,[56,57] socioeconomics[58] or environmental economics,[59,60] the role of social media;[61,62] and without taking into account sectors more or less remoted from healthcare such as food and beverage manufacturing, agricultural productivity or service providing businesses. Since food is at the heart of physical, mental, social and societal health, this extensive interplay between nutrition economics and a wide range of human activities does not come as a surprise, but it further complicates the picture. In the extremely challenging context of daily health maintenance, it is regrettable that health economists have still not integrated nutrition as a powerful health technology; a *statu quo* that is also reflected by the yearly conference programs of the two major international societies in health economics and health technology evaluations, HTAi and ISPOR, where the focus of the very few nutrition topics addressed remain limited to the patient context.

PROSPECTS AND PERSPECTIVES

Healthcare authorities and policymakers are well aware that chronic disease conditions associated with eating behaviour and other lifestyle patterns are a threat for the sustainability of health structures and for the wellbeing of the general population, as also for the individual citizen. This notwithstanding, the results of the numerous preventive health policies implemented since the first WHO rapport "Diet, nutrition and the prevention of chronic diseases" more than thirty years ago,[63] remain disappointing in spite of relentless efforts. Many other publications in the same vein have followed since, nutrition was linked to the Millennium Development Goals with the intention to shape the 21st century, replaced in 2015 by the more universal Sustainable Development Goals where nutrition is interconnected with all other global challenges.[64] Recent analyses confirm that in the field of nutrition current policies are generally falling short in achieving the anticipated health impacts.[65,66] In various areas, including household air pollution, unsafe water, child growth failure or smoking, progress has been made as reported by the Global Burden of Disease study. However, at the same time metabolic risk factors, such as high body mass index, high fasting plasma glucose and hypertension have continued to increase considerably.[67,68]

The attempts to effectively reduce these risk factors will be further jeopardized by the COVID-19 pandemic.[69] The increasing intake of ultra-processed food as part of

the daily diet raises a new threat because of the considerable risk of the associated consequences in terms of growing prevalence of non-communicable diseases.[70,71] It is also suggested that the emerging tendency of online food delivery services will affect health-promoting initiatives negatively.[72,73] Due to the COVID-pandemic, the use of these services has spread rapidly; the real devastating impact of this mode of food supply and -consumption might not be quantifiable before several years.[74,75]

Besides these aggravating environmental determinants, behavioural determinants do also seriously compromise effective and consistent adherence to the recommendations because of the difficulty to induce persisting changes in the daily eating habits of non-patient populations. Food choices are driven by lifestyle, taste, genetics, age, psychosocial and socio-economic factors, while influenced by personal perception of pleasure and convenience.[76] These elements are not necessarily rational but crucial to be taken into account when developing health promoting programs. In the absence of efficient approaches to get a grip on these drivers, strategies for inducing healthier eating patterns among the general population have mainly concentrated on package labels, health warnings accompanying food advertisements, subsidies to encourage purchase of healthy food, taxation of unhealthy products, and other interventions related to the food environment.[77,78] Whereas this has contributed to an improved general awareness about the importance of nutrition and triggered more interest in the relationship between food and health, the phenomenon has been recognized by the food- and supplement-business as a lucrative vantage point to praise the deliciousness of mouthwatering snacks or the power of health-enhancing superfood products. More and more commercial companies have taken interest in internet as a means to complement the classical advertisements for their brands; or for creating a relationship of trust between consumers and so-called influencers who invade websites. In some cases, these allegedly independent and frequently followed bloggers are behind the scene rewarded for disseminating messages that have been drafted and finetuned by industry-employed marketing specialists.[79] The induced purchase impulses are difficult to counter with education initiatives and communication campaigns from the competent health authorities, as they do not have the same level of appeal.

Furthermore, the general public, even though recognizing and accepting the relevance of the messages, is inclined to consider that it applies to others, not to oneself, because of (apparent) good health, oblivious of exposure to long-term risk factors and feeling unconcerned by an ailment predicted for a far-off future.[80] The absence of perceivable short-term benefits may affect motivation. In other cases, food indulgency will be justified by compensatory health beliefs.[81,82] A high number of alerts about the worrying consequences of inappropriate food intake and exhortations to modify lifestyle can

be counterproductive and lead to disengagement of the target population and even mistrust.[83]

It becomes urgent to get out of this critical situation, we cannot afford to continue "eating up" our health, thus drawing unjustifiably on scarce healthcare resources; in particular now that the pandemic has put an unprecedented strain on health care structures and provisions. The sustainable nutrition goals have become trans-generational and exceed the scope and the lifetime of the average individual. Recent studies suggest different manners and tools to promote healthy eating and balanced food habits more efficiently through information provision and nudge strategies.[84-86] Even if these may help to improve the effect of health promoting policies, it can be hypothesized that the general population will continue to be insufficiently spurred as long as people are not more directly engaged in the process of investigating and establishing the most appropriate orientation for adequate healthy eating strategies. One way to accomplish this might be the more systematic development of projects based on citizen science. Citizen science brings about cooperation and collaboration between academic specialists and voluntary individuals from the general public, combining scientific research with citizen experiences and observations from a real-world perspective.[87,88] The earliest citizen science initiatives started in the field of environmental research.[89,90] Over the last years the advent of mobile health applications and other digital wearables has facilitated and increased citizen science projects in the field of lifestyle.[91,92] In biomedical research an increasing number of citizen science studies are published.[93,94] In comparison, initiatives in the field of nutrition still represent a limited proportion of citizen science projects, but a few reports illustrate the unprecedented opportunities this approach offers.[95,96]

The deployment of citizen science within the field of nutrition economics constitutes an outstanding opportunity to get better insight in the most suitable triggers for inducing durable behaviour changes, an important challenge for health promotion as illustrated by the difficulties to reduce alcohol consumption or smoking.[97,98] It will require involvement of biomedical skills as well as psychosocial research approaches. The already existing tools and know-how in health technology assessment will facilitate the process for setting the right balance between quantitative and qualitative measurements and contribute to catalyzing an interdisciplinary skill building required for unraveling the most pertinent levers for successful healthy food promotion. Research projects may be conducted in collaboration with policymakers and other professional stakeholder parties. It would foster an interdisciplinary trans-silo study environment linking nutrition and behavioural sciences with society and science literacy.[99,100] This connection between health reforms and citizen perspectives, attitudes and experiences

has the potential to improve the understanding of the critical issues and to favour transparency.[101]

New insights as a result of integrating citizen science in nutrition economics may open unexpected dimensions and contribute to narrowing the know-to-do gap between health policies, population health and the health inequalities that hamper the implementation of successful strategies.[102,103] It appears that citizen science research allows inclusion of citizens with low socioeconomic status and other minority populations, in general underrepresented in health-related research, which often fails to account for the huge diversity in social, cultural, demographic, and geographic factors. The relevance of the collected nutrition-health data will thus be strengthened.[104,105]

The co-creation of nutritional study data is likely to engender a feeling of belonging among the citizen scientists, prompting an intrinsic motivation to informally spread the outcomes among fellow-citizens, a form of peer advocacy resulting in a better uptake of the recommendations that will be regarded more relevant or trustworthy. Improved effectiveness of the implemented strategies will gradually make the general population more food literate.[106,107] This will help individuals to get a better grasp on the basic principles of balanced eating patterns and gradually exert a positive impact on healthy food choices overall. It has been shown that dietary behaviour may contribute to differences in socio-economic conditions.[108,109]

Last but not least, the acquired sense of discernment is likely to serve as a protection against internet misinformation and make people less receptive to nutritional blog posts and related messages, disseminated by marketing influencers who often lack the appropriate qualifications, while being promoted or promoting themselves as experts, providing low-quality or even misleading information and using communication techniques that arouse the interest of the internet food-surfers, with potentially harmful consequences.[110,111]

The combination of nutrition economics and citizen science will have to face many challenges. Both disciplines are young and still need to earn their credentials before gaining broad acceptance in the purview of the scientists and health practitioners as also of the decisionmakers, in general not yet accustomed to actively involve lay people in health research processes, evidence generation or in decision-sharing commitments. Some of the well-established methodologies will need to be adapted or redesigned for developing appropriate measurement tools. Practice silos of the part-taking actors will have to be pulled down and comfort zones are to be left behind. Overarching frameworks to warrant the accuracy and quality of the collected information should be

defined and rigorous science-based methods to analyze the data need to be ensured. Time-consuming aspects related to recruitment of citizen participants can be a drawback. They might need support and supervision, while organizational matters and logistics can be cumbersome. On the other hand, the multi-dimensional character of the food-environment offers the advantage of an inspiring springboard for a science-driven core-activity of innovative translational research. Among the citizen scientists there is a lot of untapped resources in terms of knowledge, interest and willingness to invest time. A diverse and inclusive team will be able to collect numerous new real-world data that would otherwise be hard to obtain. As a result, more diverse information will be available to conduct nutrition economic models with more detailed scenario-analyses, thereby broadening and strengthening the practice evidence-base to reach value-based decisions within complex socio-economic structures and global health systems. The resulting outcomes will be a major asset in shaping convincing arguments and attractive lifestyle-changing incentives for the consumer in spite of the very long-term horizon he or she will have to face.

CONCLUSION

Nutrition and public health have become a priority on all health agendas worldwide, scientific and other kind of publications on the subject have increased considerably over the past few years. The determining roles of dietary risk factors in the pathogenesis of non-communicable diseases is now generally acknowledged, they form an immense threat both for the sustainability of public health structures and for the wellbeing of the general population. The launch of nutrition economics as a new branch of health economics, ten years ago, has found a considerable resonance. It appears that the nutrition economic concept has been picked up in many different areas and in all parts of the world, addressing a high variety of topics.[112] Despite the obvious need of well-conducted analyses to facilitate evidence-informed policymaking, health economists who -in principle- span the whole health-disease continuum, have not yet incorporated nutrition as part of the mainstream thinking. The relatively high level of uncertainties in real world nutritional assessments may explain the reluctancy to include food patterns more systematically in this field of activities. It is in line with the basic viewpoint that health delivery resources are best spent at treatments or interventions where robust evidence on tangible health outcomes has been demonstrated thus ensuring accurate estimations of the cost-effectiveness ratio. A widespread and respectable principle, but in today's context obviously erroneous: according to a systematic analysis for the Global-Burden-of-Disease study across 195 countries, in 2017 the number of deaths attributable to dietary risk factors totaled 11 million citizens, associated with a huge

loss of human capital.[113] It represents an almost four-fold mortality compared to the Coronavirus death toll (n= 5,672,350 million).[114]

In the light of more than thirty years of combined but relatively vain efforts to master the worrying -and now universal- issue of dietary health determinants, the unique alliance between Nutrition Economics and Citizen Science might play a crucial role in setting the right course to reverse the seemingly unrelenting increase of metabolic, cardiovascular and other food-related non-communicable diseases and their tremendous medical and socio-economic burden. At the end, this may well be our best chance to build a future where all parties, individuals and societies will value and experience daily food as one of the keys to the fundamental right of living in adequate health and well-being.

REFERENCES

1 Huskisson E. Maggini S. Ruf M. (2007) The role of vitamins and minerals in energy metabolism and well-being. *J Int Med Res.* 35, 277–289.

2 WHO. Principles and Methods for the Assessment of Risk from Essential Trace Elements. http://www.inchem.org/documents/ehc/ehc/ehc228.htm

3 Roberts LJ. (1958) Beginnings of the recommended dietary allowances. *J Am Diet Assoc*. 34, 903-908.

4 Mejia LA. (1994) Fortification of foods: Historical development and current practices. *Food & Nutr Bull*. 15, 278-281.

5 Institute of Medicine Committee on Use of Dietary Reference Intakes in Nutrition Labeling. (2003) Dietary Reference Intakes: Guiding Principles for Nutrition Labeling and Fortification. National Academies of Sciences Press, Washington DC.

6 Cohen S, Mandel D, Mimouni FB, Marom R, Lubetzky R. (2014) Conclusiveness of the Cochrane reviews in nutrition: a systematic analysis. *Eur J Clin Nutr*. 68(2), 143-5. doi:10.1038/ejcn.2013.252

7 Lenoir-Wijnkoop I, Dapoigny M, Dubois D, van Ganse E, Gutiérrez-Ibarluzea I, Hutton J, Jones P, Mittendorf T, Poley MJ, Salminen S, Nuijten MJ. (2011) Nutrition economics - characterising the economic and health impact of nutrition. *Br J Nutr*. 105(1):157-66. doi:10.1017/S0007114510003041 6

8 Gyles CL, Lenoir-Wijnkoop I, Carlberg JG, Senanayake V, Gutierrez-Ibarluzea I, Poley MJ, Dubois D, Jones PJ. (2012) Health economics and nutrition: a review of published evidence *Nutr Rev* 70(12), 693-708. doi:10.1111/j.1753-4887.2012.00514.x

9 Heaney RP. (2008) Nutrients, endpoints, and the problem of proof. *J Nutr.* 138(9), 1591-5. doi:10.1093/jn/138.9.1591

10 Weenen TC, Commandeur H, Claassen E. (2014) A critical look at medical nutrition terminology and definitions. *Trends Food Sci Technol* 38, 34e46.

11 Freijer K, Volger S, Pitter JG, Molsen-David, Cooblall C, Evers S, Hiligsmann M, Danel A, Lenoir-Wijnkoop I. (2019) Medical Nutrition Terminology and Regulations in the United States and Europe - A Scoping Review: Report of the ISPOR Nutrition Economics Special Interest Group. *Value Health*. 22(1), 1-12.

12 Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, Compher C, Correia I, Higashiguchi T, Holst M, Jensen GL, Malone A, Muscaritoli M, Nyulasi I, Pirlich M, Rothenberg E, Schindler K, Schneider SM, de van der Schueren MA, Sieber C, Valentini L, Yu JC, Van Gossum A, Singer P. (2017) ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr*. 36, 49e64.

13 Freijer K, Lenoir-Wijnkoop I, Russell CA, Koopmanschap MA, Kruizenga HM, Lhachimi SK, Norman K, Nuijten MJ, Schols JM. (2015) The view of European experts regarding health economics for medical nutrition in disease-related malnutrition. *Eur J Clin Nutr*. 69(5), 539-45. doi:10.1038/ejcn.2014.280

14 de van der Schueren M, Elia M, Gramlich L, Johnson MP, Lim SL, Philipson T, Jaferi A, Prado CM. (2014) Clinical and economic outcomes of nutrition interventions across the continuum of care. *Ann N Y Acad Sci.* 1321, 20-40. doi:10.1111/nyas.12498

15 Nuijten M, Lenoir-Wijnkoop I. (2011) Nutrition economics: an innovative approach to informed public health management. *Eur J Pharmacol*. 668 Suppl 1, S133-7. doi:10.1016/j.ejphar.2011.07.010

16 Sach TH, McManus E, Levell NJ. (2019) Understanding economic evidence for the prevention and treatment of atopic eczema. *Br J Dermatol*. 181(4), 707-716. doi: 10.1111/bjd.17696

17 Guest JF, Kobayashi RH, Mehta V, Neidich G. (2018) Cost-effectiveness of using an extensively hydrolyzed casein formula containing *Lactobacillus rhamnosus* GG in managing infants with cow's milk allergy in the US. *Curr Med Res Opin*. 34(9), 1539-1548. doi:10.1080/03007995.2017.1400962

18 Martins R, Connolly MP, Minshall E. (2021) Cost-effectiveness Analysis of Hypoallergenic Milk Formulas for the Management of Cow's Milk Protein Allergy in the United Kingdom. *J Health Econ Outcomes Res*. 8(2), 14-25. doi:10.36469/jheor.2021.26010. Erratum in: *J Health Econ Outcomes Res*. 8(2), 63

19 Zanganeh M, Jordan M, Mistry H. (2021) A systematic review of economic evaluations for donor human milk versus standard feeding in infants. *Matern Child Nutr*. 17(2), e13151. doi:10.1111/mcn.13151

20 Vandenplas Y, Hauser B, Salvatore S. (2019) Functional Gastrointestinal Disorders in Infancy: Impact on the Health of the Infant and Family. *Pediatr Gastroenterol Hepatol Nutr*. 22(3), 207-216. doi:10.5223/pghn.2019.22.3.207

21 Mahon J, Lifschitz C, Ludwig T, Thapar N, Glanville J, Miqdady M, Saps M, Quak SH, Lenoir Wijnkoop I, Edwards M, Wood H, Szajewska H. (2017) The costs of functional gastrointestinal disorders and related signs and symptoms in infants: a systematic literature review and cost calculation for England. *BMJ Open* 7(11), e015594. doi:10.1136/bmjopen-2016-015594

22 Salvatore S, Barberi S, Borrelli O, Castellazzi A, Di Mauro D, Di Mauro G, Doria M, Francavilla R, Landi M, Martelli A, Miniello VL, Simeone G, Verduci E, Verga C, Zanetti MA, Staiano A; SIPPS Working Group on FGIDs. (2016) Pharmacological interventions on early functional gastrointestinal disorders. *Ital J Pediatr*. 42(1), 68. doi:10.1186/s13052-016-0272-5

23 Harrison M, Fraser R, Mullan B. (1961) Calcium metabolism in osteoporosis: acute and long-term responses to increased calcium intake. *Lancet* 1(1015), 681.

24 Owen RA, Melton LJ 3rd, Gallagher JC, Riggs BL. (1980) The national cost of acute care of hip fractures associated with osteoporosis. *Clin Orthop Relat Res*. 150, 172-6.

25 Wingate MB. (1984) Postmenopausal osteoporosis: concerns and costs in clinical management. *J Med*. 15(4), 323-32.

26 Tosteson AN, D I Rosenthal DI, Melton 3rd LJ, Weinstein MC. (1990) Cost effectiveness of screening perimenopausal white women for osteoporosis: bone densitometry and hormone replacement therapy. *Ann Intern Med*. 113(8), 594-603. doi:10.7326/0003-4819-113-8-594

27 Gabriel SE, Kneeland TS, Melton 3rd LJ, Moncur MM, Ettinger B, Tosteson AN. (1999) Health-related quality of life in economic evaluations for osteoporosis: whose values should we use? *Med Decis Making* 19(2), 141-8. doi:10.1177/0272989X9901900204

28 Hiligsmann, M., Neuprez, A., Buckinx, F., Locquet, M., & Reginster, J. Y. (2017). A scoping review of the public health impact of vitamin D-fortified dairy products for fracture prevention. *Archives of osteoporosis* 12(1), 57. https://doi.org/10.1007/s11657-017-0352-1

29 Lips P, Bouillon R, van Schoor NM, Vanderschueren D, Verschueren S, Kuchuk N, Milisen K, Boonen S. (2010) Reducing fracture risk with calcium and vitamin D. *Clin Endocrinol (Oxf)*. 73(3), 277-85. doi:10.1111/j.1365-2265.2009.03701.x

30 Hiligsmann M, Fardellone P, Reginster JY. (2018) Promoting the consumption of dairy products for fracture prevention: A good value for money? *Joint Bone Spine* 85, 403–404.

31 Doidge JC, Segal L, Gospodarevskaya E. (2012) Attributable risk analysis reveals potential healthcare savings from increased consumption of dairy products. *J Nutr*. 142(9), 1772-80.

32 Javanbakht M, Jamshidi AR, Baradaran HR, Mohammadi Z, Mashayekhi A, Shokraneh F, Rezai Hamami M, Yazdani Bakhsh R, Shabaninejad H, Delavari S, Tehrani A. (2018) Estimation and Prediction of Avoidable Health Care Costs of Cardiovascular Diseases and Type 2 Diabetes Through Adequate Dairy Food Consumption: A Systematic Review and Micro Simulation Modeling Study. *Arch Iran Med*. 21(5), 213-222.

33 Scrafford CG, Bi X, Multani JK, Murphy MM, Schmier JK, Barraj LM. (2020) Health Care Costs and Savings Associated with Increased Dairy Consumption among Adults in the United States. *Nutrients* 12(1), 233. doi:10.3390/nu12010233

34 Sniffen JC, McFarland LV, Evans CT, Goldstein EJC. (2018) Choosing an appropriate probiotic product for your patient: An evidence-based practical guide. *PLoS One* 13(12), e0209205. doi:10.1371/journal.pone.0209205

35 Agamennone V, Krul CAM, Rijkers G, Kort R. (2018) A practical guide for probiotics applied to the case of antibiotic-associated diarrhea in The Netherlands. *BMC Gastroenterol*. 18(1), 103. doi:10.1186/s12876-018-0831-x

36 Vermeersch SJ, Vandenplas Y, Tanghe A, Elseviers M, Annemans L. (2018) Economic evaluation of *S. boulardii* CNCM I-745 for prevention of antibiotic associated diarrhoea in hospitalized patients. *Acta Gastroenterol Belg*. 81(2), 269-276.

37 Karl JP. (2021) Gut Microbiota-targeted Interventions for Reducing the Incidence, Duration, and Severity of Respiratory Tract Infections in Healthy Non-elderly Adults. *Mil Med*. 186(3-4), e310-e318. doi:10.1093/milmed/usaa261

38 Abdullah MMH, Marinangeli CPF, Jones PJH, Carlberg JG. (2017) Canadian Potential Healthcare and Societal Cost Savings from Consumption of Pulses: A Cost-Of-Illness Analysis. *Nutrients* 9(7), 793. doi:10.3390/nu9070793

39 Murphy MM, Schmier JK. (2020) Cardiovascular Healthcare Cost Savings Associated with Increased Whole Grains Consumption among Adults in the United States. *Nutrients* 12(8), 2323. doi:10.3390/nu12082323

40 Abdullah MMH, Hughes J, Grafenauer S. (2021) Whole Grain Intakes Are Associated with Healthcare Cost Savings Following Reductions in Risk of Colorectal Cancer and Total Cancer Mortality in Australia: A Cost-of-Illness Model. *Nutrients* 13(9), 2982. doi:10.3390/nu13092982

41 https://ec.europa.eu/eurostat/fr/web/products-eurostat-news/-/ddn-20210118-1. Accessed 23 January 2022

42 https://www.healthsystemtracker.org/chart-collection/what-do-we-know-about-spending-related-to-public-health-in-the-u-s-and-comparable-countries/. Accessed 23 January 23 2022

43 O'Rourke B, Oortwijn W, Schuller T. (2020) The new definition of health technology assessment: a milestone in international collaboration. *Int J Technol Assess Health Care* 36,187–90. doi:10.1017/S0266462320000215

44 Wübbeler M, Geis S, Stojanovic J, Elliott L, Gutierrez-Ibarluzea I, Lenoir-Wijnkoop I. (2021) Coding Public Health Interventions for Health Technology Assessments: A Pilot Experience With WHO's International Classification of Health Interventions (ICHI). *Front Public Health* 2021 9, 620637. doi:10.3389/fpubh.2021.620637

45 Stojanovic J, Wübbeler M, Geis S, Reviriego E, Gutiérrez-Ibarluzea I, Lenoir-Wijnkoop I. (2020) Evaluating Public Health Interventions: A Neglected Area in Health Technology Assessment. *Front Public Health* 2020 Apr 22;8:106. doi:10.3389/fpubh.2020.00106

46 Loewen OK, Ekwaru JP, Ohinmmaa A, Veugelers PJ. (2019) Economic Burden of Not Complying with Canadian Food Recommendations in 2018. *Nutrients* 11(10), 2529. doi:10.3390/nu11102529

47 Scrafford CG, Bi X, Multani JK, Murphy MM, Schmier JK, Barraj LM. (2018) Health Economic Evaluation Modeling Shows Potential Health Care Cost Savings with Increased Conformance with Healthy Dietary Patterns among Adults in the United States. *J Acad Nutr Diet*. 119(4), 599-616. doi:10.1016/j.jand.2018.10.002

48 Bauer S, Bilić S, Reetz C, Ozer F, Becker K, Eschenbeck H, Kaess M, Rummel-Kluge C, Salize HJ, Diestelkamp S, Moessner M; ProHEAD Consortium. (2019) Efficacy and cost-effectiveness of Internet-based selective eating disorder prevention: study protocol for a randomized controlled trial within the ProHEAD Consortium. *Trials* 20(1), 91. doi:10.1186/s13063-018-3161-y

49 Brown A, Sutherland R, Reeves P, Nathan N, Wolfenden L. (2021) Cost and Cost Effectiveness of a Pilot m-Health Intervention Targeting Parents of School-Aged Children to Improve the Nutritional Quality of Foods Packed in the Lunchbox. *Nutrients*. 13(11), 4136. doi:10.3390/nu13114136

50 Mozaffarian D, Liu J, Sy S, Huang Y, Rehm C, Lee Y, Wilde P, Abrahams-Gessel S, de Souza Veiga Jardim T, Gaziano T, Micha R. (2018) Cost-effectiveness of financial incentives and disincentives for improving food purchases and health through the US Supplemental Nutrition Assistance Program (SNAP): A microsimulation study. *PLoS Med*. 15(10), e1002661. doi:10.1371/journal.pmed.1002661

51 Carter HE, Schofield DJ, Shrestha R, Veerman L. (2019) The productivity gains associated with a junk food tax and their impact on cost-effectiveness. *PLoS One* 14(7), e0220209. doi:10.1371/journal.pone.0220209

52 Lyerly R, Rummo P, Amin S, Evans W, Cohen ED, Lawson E, Hallett E, De-Oliveira S, Rose J, Sutten Coats C, Nunn A. (2020) Effectiveness of mobile produce markets in increasing access and affordability of fruits and vegetables among low-income seniors. *Public Health Nutr*. 23(17), 3226-3235. doi:10.1017/S1368980020002931

53 Griffiths ML, Powell E, Usher L, Boivin J, Bott L. (2020) The health benefits and cost-effectiveness of complete healthy vending. *PLoS One* 15(9), e0239483. doi:10.1371/journal.pone.0239483

54 Giacobone G, Tiscornia MV, Guarnieri L, Castronuovo L, Mackay S, Allemandi L. (2021) Measuring cost and affordability of current *vs*. healthy diets in Argentina: an application of linear programming and the INFORMAS protocol. *BMC Public Health* 21(1):891. doi:10.1186/s12889-021-10914-6

55 Lee AJ, Kane S, Lewis M, Good E, Pollard CM, Landrigan TJ, Dick M. (2018) Healthy diets ASAP - Australian Standardised Affordability and Pricing methods protocol. *Nutr J.* 17(1), 88. doi:10.1186/s12937-018-0396-0

56 Cory M, Loiacono B, Clark Withington M, Herman A, Jagpal A, Buscemi J. (2021) Behavioral Economic Approaches to Childhood Obesity Prevention Nutrition Policies: A Social Ecological Perspective. *Perspect Behav Sci*. 44(2-3), 317-332. doi:10.1007/s40614-021-00294-y

57 Shearer J, Kalyani M, Mangelis A, de Silva D, de Silva P, Wijesuriya M, Karalliedde J. (2021) Cost-Effectiveness of Peer-Educator-Delivered Lifestyle Modification for Type 2 Diabetes Prevention in a Young Healthy Population in Sri Lanka: A Trial-Based Economic Evaluation and Economic Model. *Pharmacoecon Open* 5(4), 693-700. doi:10.1007/s41669-021-00284-5

58 Lancsar E, Ride J, Black N, Burgess L, Peeters A. (2022) Social acceptability of standard and behavioral economic inspired policies designed to reduce and prevent obesity. *Health Econ*. 31(1), 197-214. doi:10.1002/hec.4451

59 de Pee S, Hardinsyah R, Jalal F, Kim BF, Semba RD, Deptford A, Fanzo JC, Ramsing R, Nachman KE, McKenzie S, Bloem MW. (2021) Balancing a sustained pursuit of nutrition, health, affordability and climate goals: exploring the case of Indonesia. *Am J Clin Nutr*. 114(5), 1686-1697. doi:10.1093/ajcn/nqab258

60 Hobbs DA, Durrant C, Elliott J, Givens DI, Lovegrove JA. (2020) Diets containing the highest levels of dairy products are associated with greater eutrophication potential but higher nutrient intakes and lower financial cost in the United Kingdom. *Eur J Nutr*. 59(3), 895-908. doi:10.1007/s00394-019-01949-y

61 Tatlow-Golden M, Parker D. (2020) The Devil is in the Detail: Challenging the UK Department of Health's 2019 Impact Assessment of the Extent of Online Marketing of Unhealthy Foods to Children. *Int J Environ Res Public Health* 17(19), 7231. doi:10.3390/ijerph17197231

62 Sacks G, Looi ESY. (2020) The Advertising Policies of Major Social Media Platforms Overlook the Imperative to Restrict the Exposure of Children and Adolescents to the Promotion of Unhealthy Foods and Beverages. Int J *Environ Res Public Health* 17(11), 4172. doi:10.3390/ijerph17114172

63 WHO Study Group. Diet, Nutrition, and the prevention of chronic diseases. (1990) World Health Organization Technical Report Series 797, Geneva.

64 Lopez de Romaña D, Greig A, Thompson A, Arabi M. (2021) Successful delivery of nutrition programs and the sustainable development goals. *Curr Opin Biotechnol*. 70, 97-107. doi:10.1016/j.copbio.2021.03.004

65 Sisnowski J, Street JM, Merlin T. (2017) Improving food environments and tackling obesity: A realist systematic review of the policy success of regulatory interventions targeting population nutrition. *PLoS One* 12(8), e0182581. doi:10.1371/journal.pone.0182581

66 Moz-Christofoletti MA, Wollgast J. (2021) Sugars, Salt, Saturated Fat and Fibre Purchased through Packaged Food and Soft Drinks in Europe 2015-2018: Are We Making Progress? *Nutrients* 13(7), 2416. doi:10.3390/nu13072416

67 GBD 2019 Risk Factors Collaborators. (2020) Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020 396(10258), 1223-1249. doi:10.1016/S0140-6736(20)30752-2

68 https://www.healthdata.org/news-release/lancet-latest-global-disease-estimates-reveal-perfect-storm-rising-chronic-diseases-and

69 Ribeiro-Silva RC, Pereira M, Aragão É, Guimarães JMM, Ferreira AJF, Rocha ADS, Silva NJ, Teixeira CSS, Falcão IR, Paixao ES, Barreto ML. (2021) COVID-19, Food Insecurity and Malnutrition: A Multiple Burden for Brazil. *Front Nutr*. 8, 751715. doi:10.3389/fnut.2021.751715

70 Sobba W, Landry MJ, Cunanan KM, Marcone A, Gardner CD. (2021) Changes in Ultra-Processed Food Consumption and Lifestyle Behaviors Following COVID-19 Shelter-in-Place: A Retrospective Study. *Foods* 10(11), 2553. doi:10.3390/foods10112553

71 Lane MM, Davis JA, Beattie S, Gómez-Donoso C, Loughman A, O'Neil A, Jacka F, Berk M, Page R, Marx W, Rocks T. (2021) Ultraprocessed food and chronic noncommunicable diseases: A systematic review and meta-analysis of 43 observational studies. *Obes Rev.* 22(3), e13146. doi:10.1111/obr.13146

72 Poelman MP, Thornton L, Zenk SN. (2020) A cross-sectional comparison of meal delivery options in three international cities. *Eur J Clin Nutr.* 74, 1465–1473.

73 Jia SS, Gibson AA, Ding D, Allman-Farinelli M, Phongsavan P, Redfern J, Partridge SR. Perspective: Are Online Food Delivery Services Emerging as Another Obstacle to Achieving the 2030 United Nations Sustainable Development Goals? (2022) *Front Nutr.* 9, 858475. doi:10.3389/fnut.2022.858475

74 Wang XC, Kim W, Holguín-Veras J, Schmid J. (2021) Adoption of delivery services in light of the COVID pandemic: Who and how long? *Transp Res Part A Policy Pract*. 154, 270-286. doi:10.1016/j.tra.2021.10.012

75 Jia SS, Raeside R, Redfern J, Gibson AA, Singleton A, Partridge SR. (2021) #SupportLocal: how online food delivery services leveraged the COVID-19 pandemic to promote food and beverages on Instagram. *Public Health Nutr*. 24(15),4812-4822. doi:10.1017/S1368980021002731

76 Munt AE, Partridge SR, Allman-Farinelli M. (2017) The barriers and enablers of healthy eating among young adults: a missing piece of the obesity puzzle: A scoping review. *Obes Rev*. 18(1), 1-17. doi:10.1111/obr.12472

77 Song J, Brown MK, Tan M, MacGregor GA, Webster J, Campbell NRC, Trieu K, Ni Mhurchu C, Cobb LK, He FJ. (2021) Impact of color-coded and warning nutrition labelling schemes: A systematic review and network meta-analysis. *PLoS Med*. 18(10), e1003765. doi:10.1371/journal.pmed.1003765

78 von Philipsborn P, Stratil JM, Burns J, Busert LK, Pfadenhauer LM, Polus S, Holzapfel C, Hauner H, Rehfuess E. (2019) Environmental interventions to reduce the consumption of sugar-sweetened beverages and their effects on health. *Cochrane Database Syst Rev*. 6(6),CD012292. doi:10.1002/14651858.CD012292.pub2

79 Oliveira M, Barbosa R, Sousa A. (2020). The Use of Influencers in Social Media Marketing. In: Rocha Á, Reis J, Peter, M, Bogdanović Z. (eds) Marketing and Smart Technologies. Smart Innovation, Systems and Technologies, vol 167. Springer, Singapore.

80 Diepeveen S, Ling T, Suhrcke M, Roland M, Marteau TM. (2013) Public acceptability of government intervention to change health-related behaviours: a systematic review and narrative synthesis. *BMC Public Health* 13, 756. doi:10.1186/1471-2458-13-756.

81 Shepherd R. (2002) Resistance to changes in diet. *Proceedings of the Nutrition Society* 61, 267-272.

82 Prinsen S, Evers C, de Ridder DTD. (2019) Justified indulgence: self-licensing effects on caloric consumption. *Psychol Health* 34(1), 24-43. doi:10.1080/08870446.2018.1508683.

83 Bergman K, Eli K, Osowski CP, Lövestam E, Nowicka P. (2019) Public Expressions of Trust and Distrust in Governmental Dietary Advice in Sweden. *Qual Health Res.* 29(8), 1161-1173. doi:10.1177/1049732318825153.

84 Evers C, Marchiori DR, Junghans AF, Cremers J, De Ridder DTD. (2018) Citizen approval of nudging interventions promoting healthy eating: the role of intrusiveness and trustworthiness. *BMC Public Health* 18(1), 1182. doi:10.1186/s12889-018-6097-y

85 Broers VJV, De Breucker C, Van den Broucke S, Luminet O. (2017) A systematic review and meta-analysis of the effectiveness of nudging to increase fruit and vegetable choice. *Eur J Public Health* 27(5),912-920. doi:10.1093/eurpub/ckx085

86 Abrahamse W. (2020) How to Effectively Encourage Sustainable Food Choices: A Mini-Review of Available Evidence. *Front Psychol*. 11, 589674. doi:10.3389/fpsyg.2020.589674

87 Irwin A. (2018) No PhDs needed: how citizen science is transforming research. *Nature* 562, 480-482.

88 Statements of the science academies. (2019) Citizen science in the Internet era. Summit of the G7 2019. https://www.academie-sciences.fr/pdf/rapport/Citizen_G7_2019_EN.pdf

89 Merenlender AM, Crall AW, Drill S, Prysby M, Ballard H. (2016) Evaluating environmental education, citizen science, and stewardship through naturalist programs. *Conserv Biol.* 30(6), 1255-1265. doi:10.1111/cobi.12737

90 Sherbinin A, Bowser A, Chuang T, Cooper C, Danielsen F, Edmunds R, Elias P, Faustman E, Hultquist C, Mondardini R, Popescu I, Shonowo A, Sivakumar K. (2021) The Critical Importance of Citizen Science Data. *Frontiers in Climate* 3, 650760.

91 King AC, Winter SJ, Sheats JL, Rosas LG, Buman MP, Salvo D, Rodriguez NM, Seguin RA, Moran M, Garber R, Broderick B, Zieff SG, Sarmiento OL, Gonzalez SA, Banchoff A, Dommarco JR.

(2016) Leveraging Citizen Science and Information Technology for Population Physical Activity Promotion. *Transl J Am Coll Sports Med*. 1(4), 30-44.

92 Katapally TR, Chu LM. (2020) Digital epidemiological and citizen science methodology to capture prospective physical activity in free-living conditions: a SMART Platform study. *BMJ Open* 10(6), e036787. doi:10.1136/bmjopen-2020-036787

93 Schaaf J, Neff M, Scheidt J, Steglich M, Storf H. (2021) Citizen Science in Human Medicine and the Use of Software-Systems: A Rapid Scoping Review. *Stud Health Technol Inform*. 283, 172-179. doi:10.3233/SHTI210557

94 De Boeck I, Wittouck S, Wuyts S, Oerlemans EFM, van den Broek MFL, Vandenheuvel D, Vanderveken O, Lebeer S. (2017) Comparing the Healthy Nose and Nasopharynx Microbiota Reveals Continuity as well as Niche-Specificity. *Front Microbiol*. 8, 2372. doi:10.3389/fmicb.2017.02372

95 Cade JE. (2017) Measuring diet in the 21st century: use of new technologies. *Proc Nutr Soc*. 76(3), 276-282. doi:10.1017/S0029665116002883

96 Alshurafa N, Lin AW, Zhu F, Ghaffari R, Hester J, Delp E, Rogers J, Spring B. (2019) Counting Bites with Bits: Expert Workshop Addressing Calorie and Macronutrient Intake Monitoring. *J Med Internet Res*. 21(12), e14904. doi:10.2196/14904

97 Zimmerman GL, Olsen CG, Bosworth MF. (2000) A 'Stages of Change' Approach to Helping Patients Change Behavior. *Am Fam Physician* 61(5), 1409-1416.

98 Kelly MP, Barker M. (2016) Why is changing health-related behaviour so difficult? *Public Health* 136, 109-116.

99 Chrisinger BW, Ramos A, Shaykis F, Martinez T, Banchoff AW, Winter SJ, King AC. (2018) Leveraging Citizen Science for Healthier Food Environments: A Pilot Study to Evaluate Corner Stores in Camden, New Jersey. *Front Public Health* 6, 89. doi:10.3389/fpubh.2018.00089

100 Sheats JL, Winter SJ, Romero PP, King AC. (2017) FEAST: Empowering Community Residents to Use Technology to Assess and Advocate for Healthy Food Environments. *J Urban Health* 94(2), 180-189. doi:10.1007/s11524-017-0141-6

101 Bonney R, Cooper C, Ballard H. (2016). The Theory and Practice of Citizen Science: Launching a New Journal. *Citizen Science: Theory and Practice*, 1(1), 1. doi:http://doi.org/10.5334/cstp.65

102 Theobald S, Brandes N, Gyapong M, El-Saharty S, Proctor E, Diaz T, Wanji S, Elloker S, Raven J, Elsey H, Bharal S, Pelletier D, Peters DH. (2018) Implementation research: new imperatives and opportunities in global health. *Lancet* 392(10160), 2214-2228. doi:10.1016/S0140-6736(18)32205-0

103 Dahm MR, Brown A, Martin D, Williams M, Osborne B, Basseal J, Potter M, Hardie RA, Li J, Thomas J, Georgiou A. (2019) Interaction and innovation: practical strategies for inclusive consumer-driven research in health services. *BMJ Open* 9(12), e031555. doi:10.1136/bmjopen-2019-031555

104 Rajamani G, Rodriguez Espinosa P, Rosas LG. (2021) Intersection of Health Informatics Tools and Community Engagement in Health-Related Research to Reduce Health Inequities: Scoping Review. *J Particip Med*. 13(3), e30062. doi:10.2196/30062

105 Rosas LG, Rodriguez Espinosa P, Montes Jimenez F, King AC. (2022) The Role of Citizen Science in Promoting Health Equity. *Annu Rev Public Health* 43, 215-234. doi:10.1146/annurev-publhealth-090419-102856

106 Krause C, Sommerhalder K, Beer-Borst S, Abel T. (2018) Just a subtle difference? Findings from a systematic review on definitions of nutrition literacy and food literacy. *Health Promot Int.* 33(3), 378-389. doi:10.1093/heapro/daw084

107 McKinnon L, Giskes K, Turrell G. (2014) The contribution of three components of nutrition knowledge to socio-economic differences in food purchasing choices. *Public Health Nutr.* 17(8), 1814-24. doi:10.1017/S1368980013002036

108 Nutbeam D. (2000) Health literacy as a public health goal: a challenge for contemporary health education and communication strategies into the 21st century. *Health Promotion Int*. 3, 259.

109 Sawyer ADM, van Lenthe F, Kamphuis CBM, Terragni L, Roos G, Poelman MP, Nicolaou M, Waterlander W, Djojosoeparto SK, Scheidmeir M, Neumann-Podczaska A, Stronks K; PEN Consortium. (2021) Dynamics of the complex food environment underlying dietary intake in low-income groups: a systems map of associations extracted from a systematic umbrella literature review. *Int J Behav Nutr Phys Act*. 18(1):96. doi:10.1186/s12966-021-01164-1

110 Bromberg M, Fitzgerald L. (2021) Under the Influence: Regulating Influencers Giving Nutrition Advice. *J Law Med.* 28(4), 1092-1104.

111 Alruwaily A, Mangold C, Greene T, Arshonsky J, Cassidy O, Pomeranz JL, Bragg M. (2020) Child Social Media Influencers and Unhealthy Food Product Placement. *Pediatrics* 146(5), e20194057. doi:10.1542/peds.2019-4057

112 Hendriks SL. (2018) Food Policy and Nutrition Economics in the SDG era. FR Tomlinson Commemorative Lecture. doi:10.1080/03031853.2018.1479974

113 GBD 2017 Diet Collaborators. (2019) Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017 *Lancet* 393(10184), 1958-1972. doi:10.1016/S0140-6736(19)30041-8

114 https://www.worldometers.info/coronavirus/coronavirus-death-toll/. Accessed 29 January 2022

Chapter 11

Summary
Samenvatting
Résumé

SUMMARY

When the concept of functional food was introduced at the end of last century, food manufacturers quickly started to take advantage of it and add health claims to their advertising messages, with the aim of influencing the purchasing behavior of consumers. Most of the time, there was no evidence of the reported health effect. In order to protect consumers against misleading or confusing information, the European Claims Regulation (EC) No 1924/2006 was introduced with the provision that health claims could only be used after formal approval by the European Commission, based on the scientific assessment of a file with substantiated evidence submitted by the manufacturer. Convinced that the proclaimed health effects could be sufficiently demonstrated by clinical studies, the food industry had already anticipated the new legislation by internalizing the skills and knowledge needed to conduct such studies. Despite the sharp increase in R&D facilities, study results often did not match the high expectations. Dossiers did not meet the required scientific level, the complexity of the process presented an additional hurdle, and in many cases the coveted approval did not come - nor the anticipated competitive advantage. At the same time, the new claims regulation offered the pharmaceutical industry the opportunity to enter a new market segment with relatively little effort, as a simple notification procedure is sufficient for marketing vitamin preparations and other dietary supplements.

From a nutritional point of view, the above-mentioned focus on health effects of specific foods and food supplements risked pushing into the background the basic principle that a balanced diet allows a healthy person to adequately meet his daily needs for macro- and micronutrients. This inspired the hypothesis that by combining nutrition research and health economic evaluation methods, better quantification of the multidimensional characteristics of daily nutrition (both conventional and functional) and associated health effects would be achieved, not only from a healthcare perspective, but also from the perspective of the general population. The resulting studies laid the foundation of this dissertation.

Chapter 1 is a general introduction, providing a brief account of the history of nutrition and the role nutrition plays in disease and health. This is followed by background information on the relatively recent development of nutrition as part of the biomedical sciences, and on the emergence of the European legislation on health claims. Finally, a brief description of the outline of this dissertation follows. **Chapters 2 and 3** report on two consensus meetings of a multidisciplinary expert panel that aimed to assess the extent to which it would be possible to bridge nutritional research with health economic principles. The scope and some methodological aspects of a new discipline

named “Nutrition Economics” are defined and the importance of this new approach in supporting efficient public health guidelines is discussed. Although it is well known that nutrition has a major influence on the burden of disease, until recently little attention was paid to the societal and individual socio-economic consequences of insufficient or unbalanced food intake in the population, partly because of the complexity of mapping the numerous factors that play a role in daily eating habits and their consequences. To gain a better understanding of this, the studies presented in this thesis are based on modelling.

Computational models make it possible to analyze diverse and multifaceted data together. Thanks to model-based studies, clinical outcomes obtained within a select study group can be extrapolated to a larger group of similar individuals in the general population. Effects, observed during the - per definition limited - study period, can thus be projected over a longer period of time. Also, the incremental impact of future changes in a health condition can be incorporated. Furthermore, a diversity of other data can be fed into the model, such as cost data (direct and indirect medical costs, non-medical costs), epidemiological data, measurements of quality of life, population statistics, the consequences of absenteeism and reduced work capacity on productivity loss, and other related socio-economic aspects. This modelling approach is fully recognized and applied within health economics to calculate the cost-effectiveness of medical interventions as well as to support decision-making in health care delivery and financing.

Chapter 4 pertains to a pilot study, the first “proof-of-concept” demonstration of the above-mentioned nutrition economics approach. Clinical data from two randomized trials in healthy newborn babies, at increased risk of allergy, were analyzed in a computer model. Apart from evaluating the direct medico-economic consequences of atopic dermatitis, an analysis was also performed based on the assumption that an infant developing atopic dermatitis is at an increased risk of asthma up to the age of 16 years. Since cost data can differ per country, this analysis focuses specifically on the situation in the Netherlands. The results show that an infant formula containing a mixture of prebiotics (indigestible food ingredients that promote the growth of healthy gut flora), compared to infant formula without prebiotics, offers a cost-effective solution for primary prevention of atopic dermatitis, with positive health and economic outcomes in the short and long term.

Chapter 5 illustrates the importance of nutrition economic evaluations from three different perspectives: 1) malnutrition associated with growth retardation, with a reduction in intellectual capacities, which has far-reaching consequences for later

socio-economic living conditions and loss of human capital; 2) the impact of poor eating habits and/or an excess of unhealthy foods - at the population level, nutritional interventions have been found to be on average considerably more cost-effective than medical interventions, medicines or vaccination; 3) the supply of selected functional food products for the maintenance of good personal health, especially in case of existing risk factors. The conclusion of this report is that health authorities and decision-makers should be more aware of the benefits of a balanced diet when determining and implementing more cost-effective health policies.

Chapter 6 addresses the link between osteoporosis and a common food item that is regularly consumed as part of the daily menu in most European countries, namely dairy products. Dairy products contain a wide variety of essential nutrients (proteins, minerals, vitamins) and represent a recognized part of a healthy diet. This study aims to quantify the health economic costs of osteoporosis, as well as the impact of increased consumption of dairy products on the reduction of osteoporotic fractures in the elderly and the associated loss of quality of life. The analysis shows that hip fractures combined with low calcium intake impose a substantial economic and social burden. These findings support the relevance of a nutritional approach to limit age-related bone loss, maintain quality of life and autonomy in the elderly, and reduce associated healthcare expenditures.

Chapter 7 deals with obesity during pregnancy. Overweight, a common health problem among young and old, is associated with an increased risk of obesity and type 2 diabetes. Consequently, it represents a steadily increasing burden on public health. The study in this chapter shows why this is a particularly worrying phenomenon for women of childbearing age; overweight in pregnant women not only leads to a higher risk of perinatal morbidity and mortality, but also to the occurrence of gestational diabetes. Gestational diabetes increases the risk of macrosomia (excessive birth weight) in the baby. This does not only increase the risk of complications around delivery, in addition it exposes the child to health risks later in life. Even without considering the long-term consequences, this study shows that the direct healthcare costs of gestational diabetes and macrosomia exceed $1.8 billion annually. It underscores the need for effective preventive measures and public health interventions in the area of lifestyle and eating habits.

The study in **Chapter 8** is in line with the previous topic and investigates the potential health impact and socioeconomic benefits of yogurt consumption with regard to type 2 diabetes. A large meta-analysis (459 790 individuals) reported that daily yogurt consumption is associated with a lower risk of developing type 2 diabetes; no such

association was seen for dairy products in general. The computer model designed for this study takes into account the different stages of development of the disease, including the long-term risk of additional morbidity symptoms and loss of quality of life. To account for country-specific data, the analysis focuses on the population of the United Kingdom, a country that has many sources of reliable health data. Assuming a causal relationship between yogurt consumption and a lower rate of diabetes cases as reported in scientific publications, the results of this study indicate that an increase of yogurt consumption by 100 g per day/person in the adult UK population provides substantial cost savings for the National Health System, as well as a significant improvement in quality of life at population level by reducing the incidence of type 2 diabetes.

Chapter 9 discusses a health problem that affects even people with healthy lifestyles and good eating habits: seasonal respiratory infections and flu-like illnesses. These types of viral illnesses are common worldwide and place a significant burden on national healthcare systems, as well as on individuals, families and society at large. Two meta-analyses, published by the Cochrane Library and by the York Health Economics Consortium, confirmed the beneficial impact of probiotics (live bacteria that have a positive effect on our health) in reducing the incidence of these flu conditions and the duration of symptoms; thereby resulting in a reduction in the use of antibiotics and a lower absenteeism. To evaluate the effect of probiotics in preventing and reducing flu symptoms, it is again crucial to take into account country-specific data and the way in which local healthcare is organized. Therefore, this chapter is divided into three sections, which, on the basis of the same computer model, report the socio-economic findings for France, Canada and the United States respectively. Apart from the fact that the analyses show significant savings for each country, regardless of different insurance and sick leave conditions, this series of studies confirms that it is possible to efficiently adapt a carefully constructed pilot model - in this case for France - for performing nutrition economic assessments in other countries.

To conclude this dissertation, the first part of **Chapter 10** describes how Nutrition Economics has gradually gained recognition since its introduction in 2011. This is based on an analysis of the scientific literature covering the period January 2012-December 2021. It provides an overview of the variety of study topics published by independent research groups and other stakeholders during this first decade. The second part of this chapter outlines a perspective for the further development of nutrition economics during the upcoming, second decade of existence.

The continuously increasing prevalence of chronic conditions, caused by risk factors associated with daily eating and other lifestyle patterns, threatens both the sustainability

of health systems as well as the prosperity of the general population and the well-being of individual citizens. There is an urgent need to make a definitive change in this situation. We cannot afford to continue "eating up" our health, resulting in excessive (but avoidable) demands on the scarce resources of healthcare; especially now that the COVID pandemic has put unprecedented pressure on healthcare structures and facilities.

Behavioral changes in physical activity and daily eating habits are the backbone of preventive public health policies, but bringing them about is a huge challenge as evidenced by, for example, the difficulties in reducing alcohol consumption or smoking. A more systematic collaboration between scientific researchers and volunteers from the general public, whether or not in coordination with government agencies and other stakeholder parties, offers in my opinion an unparalleled opportunity to better understand the subjective factors that play a key role in lifestyle and daily eating behaviour. Study projects, based on citizen science, are still quite rare within the food world, but may offer an excellent breakthrough tool for achieving stronger engagement population level. At the same time, active participation in such projects will motivate volunteers to spontaneously bring up experiences within their own professional and personal environments. In the current atmosphere of distrust of government recommendations on one hand and, on the other hand, the willingness of many to take (unverified and) unsubstantiated Internet information for granted, the interaction between citizen science and nutritional evaluation projects will help raise a better awareness of the essential importance of daily nutrition for personal well-being. This will promote a willingness to change behavior in a more sustainable way, which in the longer term will not only benefit healthcare resources, but also socio-economic conditions and the population at large.

Nutritional literacy is the beginning of a healthier and socially more equitable world.

SAMENVATTING

Toen eind vorige eeuw het begrip functionele voeding zijn intrede deed, begonnen voedselproducenten er al snel op in te spelen en hun reclameboodschappen te voorzien van gezondheidsclaims, met als doel het koopgedrag van consumenten te beïnvloeden. Meestal was er geen bewijs geleverd van het vermelde gezondheidseffect. Om de consument te beschermen tegen misleidende of verwarrende informatie werd de Europese Claimsverordening (EC) No 1924/2006 ingevoerd met de bepaling dat gezondheidsclaims uitsluitend gebruikt konden worden na formele goedkeuring door de Europese Commissie op grond van de wetenschappelijke beoordeling van een door de fabrikant ingediend dossier met onderbouwde bewijsvoering. In de overtuiging dat de veronderstelde gezondheidseffecten voldoende zouden kunnen worden aangetoond door klinische studies, was de levensmiddelenindustrie al vooruitgelopen op de nieuwe wetgeving door het internaliseren van de vaardigheden en kennis benodigd om dergelijke onderzoeken uit te voeren. Ondanks de forse toename in R&D-faciliteiten, kwamen de onderzoeksresultaten vaak niet overeen met de hooggespannen verwachtingen. Dossiers voldeden niet aan het vereiste wetenschappelijk niveau, de complexiteit van het proces vormde een bijkomende hindernis en in veel gevallen bleef de felbegeerde goedkeuring uit – en daarmee het geanticipeerde concurrentievoordeel. Tegelijkertijd bood de nieuwe claimsverordening de farmaceutische industrie de mogelijkheid om met relatief weinig inspanning een nieuwe marktsegment in te nemen, aangezien er voor het op de markt brengen van vitaminepreparaten en andere voedingssupplementen kan worden volstaan met een simpele meldingsprocedure.

Vanuit voedingskundig oogpunt brengt de bovengenoemde focus op gezondheidseffecten van specifieke levensmiddelen en voedingssupplementen het risico met zich mee het basisbeginsel dat de gezonde mens door een evenwichtig voedingspatroon op toereikende wijze in zijn dagelijkse behoefte aan macro- en micronutriënten voorziet, op de achtergrond te dringen. Deze overweging inspireerde de hypothese dat een combinatie van voedingsonderzoek en gezondheidseconomische evaluatiemethodes het mogelijk zou maken de multidimensionale kenmerken van dagelijkse voeding (zowel conventionele als functionele) en geassocieerde gezondheidseffecten beter te kwantificeren, niet alleen vanuit het perspectief van de gezondheidszorg, maar ook vanuit het oogpunt van de algemene bevolking. De daaruitvloeiende studies legden de grondslag voor dit proefschift.

Hoofdstuk 1 is een algemene inleiding, die een korte uiteenzetting geeft van de geschiedenis van voeding en de rol die voeding speelt in ziekte en gezondheid. Dan volgt achtergrondinformatie over de betrekkelijk recente ontwikkeling van

voeding als onderdeel van de biomedische wetenschappen, en over het ontstaan van de Europese wetgeving betreffende gezondheidsclaims. Tot slot volgt een korte beschrijving van de opzet van dit proefschrift. De **hoofdstukken 2** en **3** brengen verslag uit van twee consensusbijeenkomsten van een multidisciplinair expert panel dat als doel had te beoordelen in hoeverre het mogelijk zou zijn een brug te slaan tussen voedingsonderzoek en gezondheidseconomische principes. Het toepassingsgebied en een aantal methodologische aspecten van een nieuw vakgebied "Nutrition Economics" worden gedefiniëerd en het belang van deze nieuwe discipline ter ondersteuning van efficiënte richtlijnen voor de volksgezondheid komt aan de orde. Hoewel algemeen bekend is dat voeding een grote invloed heeft op de ziektelast, werd tot voor kort weinig aandacht besteed aan de maatschappelijke en individuele socio-economische gevolgen van onvoldoende of ongezonde voedselinname van de bevolking, mede vanwege de complexiteit van het in kaart brengen van de talrijke factoren die meespelen in de dagelijkse eetgewoonten en de consequenties ervan. Om hier een beter inzicht in te krijgen, zijn de in dit proefschrift gepresenteerde studies gebaseerd op een modelmatige benadering. Computermodellen maken het mogelijk om uiteenlopende en veelzijdige gegevens gezamelijk te analyseren. Dankzij modelmatige studies kunnen klinische uitkomsten, verkregen binnen een selecte studiegroep, geëxtrapoleerd worden naar een grotere groep van vergelijkbare personen onder de bevolking. Effecten, waargenomen tijdens de - per definitie beperkte - studieperiode, kunnen hierdoor over een langere termijn worden geprojecteerd. Ook kan de incrementele impact van toekomstige veranderingen van een gezondheidstoestand worden geïncorporeerd; verder kan een diversiteit van andere gegevens in het model worden ingevoerd, zoals kostendata (directe en indirecte medische kosten, niet-medische kosten), epidemiologische data, metingen van levenskwaliteit, bevolkingsstatistieken, de gevolgen van ziekteverzuim en verminderde arbeidscapaciteiten op productiviteitsverlies en andere gerelateerde socio-economische aspecten. Deze modelmatige benadering is algemeen erkend en wordt binnen de gezondheidseconomie toegepast om zowel de kosteneffectiviteit van medische interventies te berekenen als ook ter ondersteuning van besluitvorming in de zorgverlening en -financiering.

Hoofdstuk 4 is gewijd aan een pilot-studie, de eerste "proof-of-concept" demonstratie van bovenstaande voedingseconomische benadering. Klinische gegevens, afkomstig van twee gerandomiseerde studies bij gezonde pasgeboren babies met een verhoogd risico op allergieën zijn in een computermodel geanalyseerd. Afgezien van de evaluatie van de directe medisch-economische gevolgen van atopische dermatitis, is er ook een analyse uitgevoerd op grond van de aanname dat er bij een zuigeling die atopische dermatitis ontwikkelt, tot de leeftijd van 16 jaar een verhoogd risico op astma bestaat. Aangezien kostengegevens per land kunnen verschillen, richt deze analyse zich

specifiek op de situatie in Nederland. De resultaten tonen aan dat zuigelingenvoeding met een mengsel van prebiotica (onverteerbare voedingsingrediënten die de groei van een gezonde darmflora bevorderen), in vergelijking met zuigelingenvoeding dat geen prebiotica bevat, een kosteneffectieve oplossing biedt voor de primaire preventie van atopische dermatitis, met positieve gezondheids- en economische resultaten op korte en lange termijn.

Hoofdstuk 5 illustreert het belang van voedingseconomische evaluaties aan de hand van drie verschillende invalshoeken: 1) ondervoeding die gepaard gaat met groeiachterstand, met een vermindering van intellectuele capaciteiten, en met verregaande consequenties voor latere socio-economische levensomstandigheden en een verlies van menselijk kapitaal; 2) de impact van slechte eetgewoontes en/ of een overmaat aan ongezonde levensmiddelen - op bevolkingsniveau blijken voedingsinterventies gemiddeld aanzienlijk kosteneffectiever te zijn dan medische interventies, geneesmiddelen of vaccinatie; 3) het aanbod van geselecteerde functionele voedingsproducten voor het in stand houden van een goede persoonlijke gezondheid, met name in geval van bestaande risicofactoren. De conclusie van dit rapport is dat gezondheidsautoriteiten en besluitvormers bij het bepalen en implementeren van kosteneffectievere gezondheidbeleidsmaatregelen zich beter bewust zouden moeten zijn van de voordelen van een evenwichtig voedselpatroon.

Hoofdstuk 6 analyseert het verband tussen osteoporose en een veel voorkomend voedingsmiddel dat in de meeste Europese landen regelmatig wordt geconsumeerd als onderdeel van het dagelijks menu, namelijk zuivel. Zuivelproducten bevatten een grote verscheidenheid aan essentiële voedingsstoffen (eiwitten, mineralen, vitaminen) en vertegenwoordigen een erkend onderdeel van een gezond voedingspatroon. Deze studie heeft als doel om de gezondheidseconomische kosten van osteoporose te kwantificeren, evenals de impact van een hogere consumptie van zuivelproducten op de vermindering van osteoporotische fracturen bij ouderen en het daarmee gepaard gaande verlies van levenskwaliteit. De analyse toont aan dat heupfracturen, in combinatie met een lage calciuminname, een substantiële economische en maatschappelijke last met zich meebrengen. Deze bevindingen ondersteunen de relevantie van een voedingskundige benadering om leeftijdsgebonden botverlies te beperken, de levenskwaliteit en autonomie van ouderen te handhaven, en bijbehorende zorguitgaven te verlagen.

Hoofdstuk 7 gaat in op overgewicht tijdens de zwangerschap. Overgewicht is een veelvoorkomend gezondheidsprobleem bij jong en oud, gaat gepaard met een verhoogd risico op obesitas en type 2 diabetes. Dientengevolge vertegenwoordigt het een gestaag toenemende last voor de volksgezondheid. De studie in dit hoofdstuk

toont aan waarom dit vooral voor vrouwen in de vruchtbare leeftijd een bijzonder verontrustend verschijnsel is; overgewicht bij zwangere vrouwen leidt niet alleen tot een hoger risico op perinatale morbiditeit en mortaliteit, maar ook tot het optreden van zwangerschapsdiabetes. Zwangerschapsdiabetes verhoogt de kans op macrosomie (een te hoog geboortegewicht) bij de baby. Dit leidt niet alleen tot mogelijke complicaties rond de bevalling, maar stelt het kind ook op latere leeftijd bloot aan gezondheidsrisico's. Zelfs zonder rekening te houden met de lange termijn consequenties, laat deze studie zien dat de directe kosten van zwangerschapsdiabetes en macrosomie voor de gezondheidszorg jaarlijks meer dan $1,8 miljard bedragen. Het onderstreept de noodzaak van efficiënte preventieve maatregelen en volksgezondheidsinterventies op het gebied van levensstijl en eetgewoonten.

De studie in **hoofdstuk 8** is in lijn met het voorgaande onderwerp en onderzoekt de potentiële gezondheidsimpact en socio-economische voordelen van yoghurtconsumptie met betrekking tot type 2 diabetes. Een omvangrijke meta-analyse (459 790 personen) heeft gerapporteerd dat de dagelijkse consumptie van yoghurt geassocieerd is met een lager risico om type 2 diabetes te ontwikkelen; een dergelijke associatie werd niet gezien voor zuivelproducten in het algemeen. Het voor dit onderzoek opgezette computermodel houdt rekening met de verschillende ontwikkelingsfasen van de ziekte, met inbegrip van het lange termijn risico op bijkomende morbiditeitsverschijselen en het verlies van kwaliteit van leven. Om rekening te houden met landenspecifieke gegevens, richt de analyse zich op de bevolking van het Verenigd Koninkrijk, een land dat beschikt over een groot aantal bronnen van betrouwbare gezondheidsgegevens. Uitgaande van een oorzakelijk verband tussen yoghurtconsumptie en een lager aantal diabetes gevallen als vermeld in wetenschappelijke publicaties, wijzen de resultaten van deze studie uit dat een verhoging van yoghurtconsumptie met 100 g per dag/persoon bij de volwassen Britse bevolking aanmerkelijke kostenbesparingen voor de National Health System kan opleveren, evenals een aanzienlijke verbetering van de kwaliteit van leven op bevolkingsniveau door vermindering van de incidentie van type 2 diabetes.

Hoofdstuk 9 is gewijd aan een gezondheidsprobeem dat zelfs mensen met een gezonde leefwijze en goede eetgewoontes betreft: seizoensgebonden luchtweginfecties en griepachtige ziekteverschijselen. Dit soort virale aandoeningen komen wereldwijd veel voor en vormen een aanzienlijke belasting voor nationale gezondheidszorgstelsels, maar ook voor personen, gezinnen en de maatschappij in het algemeen. Twee meta-analyses, gepubliceerd door de Cochrane Library en door de York Health Economics Consortium, bevestigden de gunstige invloed van probiotica (levende bacteriën die een positief effect hebben op onze gezondheid) op het verminderen van de incidentie van deze griepaandoeningen en van de duur van de symptomen; met daarmee een reductie

van het gebruik van antibiotica en een lager ziekteverzuim. Voor de evaluatie van het effect van probiotica bij het voorkomen en verminderen van griepverschijnselen is het wederom van cruciaal belang om rekening te houden met landenspecifieke gegevens en de wijze waarop de plaatselijke gezondheidzorg is georganiseerd. Daarom is dit hoofdstuk onderverdeeld in drie paragrafen, die op grond van eenzelfde computermodel verslag uitbrengen van de socio-economische bevindingen voor respectievelijk Frankrijk, Canada en de Verenigde Staten. Afgezien van het feit dat de analyses voor elk land aanzienlijke besparingen aantonen, los van uiteenlopende verzekerings- en ziekteverlof omstandigheden, bevestigt deze serie van studies dat het mogelijk is een zorgvuldig opgebouwd pilot model - in dit geval voor Frankrijk - efficiënt aan te passen voor het verrichten van voedingeconomische evaluaties in andere landen.

Ter afsluiting van dit proefschrift beschrijft het eerste gedeelte van **hoofdstuk 10** hoe Nutrition Economics vanaf de introductie in 2011 geleidelijk erkenning heeft verworven. Dit is gebaseerd op een analyse van de wetenschappelijke literatuur over de periode januari 2012-december 2021. Het geeft een overzicht van de verscheidenheid van studieonderwerpen die tijdens dit eerste decennium door onafhankelijke onderzoeksgroepen en andere stakeholders zijn gepubliceerd. In het tweede gedeelte van dit hoofdstuk wordt een perspectief geschetst voor de verdere ontwikkeling van voedingseconomie gedurende het komende, tweede bestaansdecennium. De onophoudelijk toenemende prevalentie van chronische aandoeningen, veroorzaakt door risicofactoren geassocieerd met dagelijks eetgedrag en andere levensstijlpatronen, bedreigt zowel de duurzaamheid van gezondheidsstelsels, als ook de welvaart van de algemene bevolking en het welzijn van de individuele burger. Het is dringend zaak om een definitieve wending aan deze situatie te geven. We kunnen het ons niet veroorloven om door te gaan met het “opeten” van onze gezondheid, als gevolg waarvan een overmatig (maar vermijdbaar) beroep wordt gedaan op de schaarse middelen binnen de zorg; zeker nu de COVID pandemie een ongekende druk heeft uitgeoefend op gezondheidszorgstructuren en -voorzieningen.

Gedragsveranderingen op het gebied van lichaamsbeweging en dagelijkse eetgewoonten vormen de ruggegraat van een preventief volksgezondheidsbeleid, maar het tot stand brengen ervan is een enorme uitdaging zoals wel blijkt uit bijvoorbeeld de problemen om alcoholgebruik of roken te verminderen. Een meer systematische samenwerking tussen wetenschappelijke onderzoekers en vrijwilligers uit het grote publiek, al dan niet in coördinatie met overheidsinstanties en andere belanghebbenden, biedt mijns inziens een ongeëvenaarde gelegenheid om een beter inzicht te krijgen in de subjectieve factoren die een sleutelrol spelen in levensstijl en dagelijkse eetgewoonten. Studieprojecten, op basis van burgerwetenschap, zijn nog vrij zeldzaam binnen de

voedingswereld, maar bieden allicht een uitstekend breekijzer voor het bewerkstelligen van een sterkere betrokkenheid op bevolkingsniveau. Tegelijkertijd zal actieve deelname aan dergelijke projecten de vrijwilligers motiveren om ervaringen spontaan ter sprake te brengen binnen hun eigen beroepsmatige en persoonlijke omgeving. In de huidige sfeer van wantrouwen ten opzichte van overheidsaanbevelingen enerzijds en, anderzijds, de bereidheid van velen om (ongecontroleerde en) ongefundeerde internetinformatie voor zoete koek te nemen, zal de interactie tussen burgerwetenschap en voedingseconomische evaluatieprojecten bijdragen aan een betere bewustwording van het essentiële belang van dagelijkse voeding voor persoonlijk welzijn. Dit zal de bereidheid tot blijvende gedragsveranderingen bevorderen, hetgeen op langere termijn niet alleen ten bate van de zorgverlening zal werken, maar ook de socio-economische omstandigheden en de bevolking in het algemeen ten goede zal komen.

Voedingsgeletterdheid is het begin van een gezondere en maatschappelijk rechtvaardigere samenleving.

RÉSUMÉ

Lorsque le concept d'aliment fonctionnel a été introduit à la fin du siècle dernier, les industriels de l'agroalimentaire ont rapidement commencé à en tirer parti en ajoutant des allégations de santé à leurs messages publicitaires, dans le but d'influencer le comportement d'achat des consommateurs. La plupart du temps, il n'y avait pas de preuve de l'effet revendiqué. Afin de protéger le consommateur contre des informations trompeuses ou prêtant à confusion, le règlement européen sur les allégations (CE) n° 1924/2006 a été introduit. Il prévoit que les allégations de santé ne peuvent être utilisées qu'après approbation formelle par la Commission européenne, sur la base de l'évaluation scientifique d'un dossier soumis par le fabricant et contenant des preuves étayées. Convaincue que les effets supposés sur la santé pouvaient être suffisamment démontrés par des études cliniques, l'industrie alimentaire avait déjà anticipé la nouvelle législation en internalisant les compétences et les connaissances requises pour mener de telles études. Malgré la forte augmentation des capacités en R&D, les résultats de ces études cliniques n'étaient souvent pas à la hauteur des attentes. Les dossiers n'atteignaient pas le niveau scientifique requis, la complexité du processus constituait un obstacle supplémentaire et, dans de nombreux cas, l'approbation tant convoitée n'était pas obtenue - ni l'avantage concurrentiel escompté. En même temps, ce nouveau règlement sur les allégations a offert à l'industrie pharmaceutique la possibilité d'entrer sur un nouveau segment de marché avec relativement peu d'efforts, car une simple procédure de notification suffit pour commercialiser des préparations vitaminées et autres compléments alimentaires.

D'un point de vue nutritionnel, l'accent mis sur les effets bénéfiques pour la santé d'un aliment ou d'un complément alimentaire spécifique risque de remettre en cause le principe de base selon lequel grâce à une alimentation équilibrée une personne en bonne santé couvre de manière adéquate ses besoins quotidiens en macro- et micronutriments. Cette considération a inspiré l'hypothèse qu'une association entre le domaine de la recherche nutritionnelle et des méthodes d'évaluation économique de santé permettrait de mieux quantifier les caractéristiques multidimensionnelles de l'alimentation quotidienne (à la fois conventionnelle et fonctionnelle) et les effets sur la santé y associés, non seulement du point de vue des soins de santé, mais aussi de celui de la population générale. Les études qui en ont résulté constituent la base de cette thèse.

Le **chapitre 1** est une introduction générale, récapitulant l'histoire de la nutrition et du rôle que joue la nutrition dans la santé et la maladie. Vient ensuite un aperçu succinct du développement relativement récent de la nutrition en tant que science

biomédicale, puis de la mise en place de la législation européenne concernant les allégations de santé. Enfin, une brève description de la structure de cette thèse est présentée. Les **chapitres 2 et 3** rendent compte de deux réunions de consensus d'un groupe d'experts multidisciplinaire visant à évaluer la possibilité de jeter un pont entre le domaine de la recherche en nutrition et les principes de l'économie de la santé. Les champs d'application et certains aspects méthodologiques d'une nouvelle discipline ''Economie de la Nutrition'' sont définis et l'intérêt de cette nouvelle discipline pour établir des directives efficaces en matière de santé publique est discuté. Bien que l'influence majeure de l'alimentation sur le poids global des maladies soit généralement reconnue, jusqu'à récemment peu d'attention a été accordée aux conséquences socio-économiques sociales et individuelles d'un apport alimentaire insuffisant ou excessif, en partie en raison de la complexité de recenser les nombreux facteurs impliqués dans les habitudes alimentaires quotidiennes et leurs corollaires. Pour mieux comprendre cet aspect, les études présentées dans cette thèse s'appuient sur une approche de modélisation.

La modélisation permet d'analyser conjointement des données diverses et polyvalentes. Grâce aux études basées sur des modèles, les résultats cliniques obtenus dans une population d'individus sélectionnés peuvent être extrapolés à un groupe plus large de sujets similaires au sein de la population générale. Les effets observés pendant la période d'étude - par définition limitée - peuvent être projetés sur une période plus longue. Il est également possible d'intégrer l'impact différentiel des changements futurs de l'état de santé ; en outre, diverses autres informations peuvent être introduites dans le modèle, telles que des données sur les coûts (coûts médicaux directs et indirects, coûts non médicaux), des données épidémiologiques, des mesures de qualité de vie, des statistiques démographiques, les conséquences de l'absentéisme et des capacités de travail réduites sur la perte de productivité, ainsi que d'autres aspects socio-économiques. Cette approche fondée sur l'utilisation d'un modèle ou d'un schéma décisionnel est largement appliquée dans le domaine de l'économie de la santé, tant pour calculer le rapport coût-efficacité des interventions médicales que pour soutenir la prise de décision en matière de prestation et de financement des soins de santé.

Le **chapitre 4** est consacré à une étude pilote, première démonstration de la preuve de concept, qui confirme la pertinence de l'approche d'Economie de la Nutrition évoquée ci-dessus. Les résultats de deux études randomisées menées chez des nouveau-nés en bonne santé, présentant un risque d'allergie, ont été analysées dans un modèle informatique. D'un part l'impact médico-économique direct de la dermatite atopique a été évalué et d'autre part, en partant de l'hypothèse qu'un enfant qui développe une dermatite atopique a un risque accru d'asthme jusqu'à l'âge de 16 ans, une deuxième

analyse a été effectué. Etant donné que les éléments relatifs aux coûts peuvent varier d'un pays à l'autre, cette analyse se concentre spécifiquement sur la situation aux Pays-Bas. Les résultats montrent qu'un lait maternisé contenant un mélange de prébiotiques (ingrédients alimentaires non digestibles qui favorisent la croissance d'une flore intestinale saine), comparé aux préparations pour nourrissons qui ne contiennent pas de prébiotiques, offre une solution rentable pour la prévention primaire de la dermatite atopique, avec des résultats positifs pour la santé et l'économie à court et à long terme.

Le **chapitre 5** illustre l'importance des évaluations économiques nutritionnelles à travers trois perspectives différentes : 1) la malnutrition associée à un retard de croissance, avec une réduction des capacités intellectuelles, et des conséquences profondes sur les conditions de vie socio-économiques ultérieures et une perte de capital humain; 2) l'impact de mauvaises habitudes alimentaires et/ou d'un excès d'aliments malsains - au niveau de la population, les interventions nutritionnelles semblent être en moyenne nettement plus rentables que les interventions médicales, les médicaments ou la vaccination; 3) l'offre de produits alimentaires fonctionnels sélectionnés pour maintenir une bonne santé personnelle, en particulier en présence de facteurs de risque existants. Le rapport conclut que les autorités sanitaires et les décideurs devraient être plus conscients des avantages d'une alimentation équilibrée lorsqu'ils déterminent et mettent en œuvre des politiques de santé.

Le **chapitre 6** analyse le lien entre l'ostéoporose et un aliment courant, régulièrement consommé dans le cadre de l'alimentation quotidienne dans la plupart des pays européens, à savoir les produits laitiers. Les produits laitiers contiennent une grande variété de nutriments essentiels (protéines, minéraux, vitamines) et font partie intégrante d'une alimentation saine. Cette étude vise à quantifier les coûts économiques de l'ostéoporose pour la santé, ainsi que l'impact d'une plus grande consommation de produits laitiers sur la réduction des fractures ostéoporotiques chez les personnes âgées et la perte de qualité de vie qu'elles entraînent. L'analyse montre que les fractures de la hanche associées à un faible apport en calcium représentent un fardeau économique et social substantiel. Ces résultats confortent la pertinence d'une approche nutritionnelle pour limiter la perte osseuse liée à l'âge, pour maintenir la qualité de vie et l'autonomie des personnes âgées et réduire les dépenses de santé associées.

Le **chapitre 7** traite de l'obésité pendant la grossesse. La surcharge pondérale est un problème de santé pour toute tranche d'âge, et elle va de pair avec un risque de développer de l'obésité, voire un diabète de type 2. De ce fait, elle représente un fardeau de plus en plus lourd pour la santé publique. L'étude présentée dans ce chapitre montre pourquoi il s'agit d'un phénomène particulièrement inquiétant chez les femmes en âge

de procréer; l'obésité chez les femmes enceintes entraîne non seulement un risque plus élevé de morbidité et de mortalité périnatales, mais aussi la survenue de diabète gestationnel. Le diabète gestationnel augmente le risque de macrosomie chez le bébé (poids excessif à la naissance). Cela entraîne non seulement d'éventuelles complications lors de l'accouchement, mais expose également l'enfant à des risques ultérieures pour sa santé. Même sans tenir compte des conséquences à long terme, cette étude montre que le coût direct du diabète gestationnel et de la macrosomie pour le système de santé s'élève à plus de $1,8 milliard par an. Elle souligne la nécessité de mesures préventives efficaces et d'interventions de santé publique dans le domaine du mode de vie et des habitudes alimentaires.

L'évaluation du **chapitre 8** s'inscrit dans le prolongement du sujet précédent et étudie la consommation de yaourt par rapport à l'impact socio-économique du diabète de type 2. Une grande méta-analyse (459 790 sujets) a rapporté que l'ingestion quotidienne de yaourt est associée à un risque plus faible de développer un diabète de type 2; aucune association de ce genre n'a été observée pour les produits laitiers en général. Le modèle informatique conçu pour cette étude prend en compte les différents stades de développement de la maladie, y compris le risque à long terme de symptômes de morbidité supplémentaires et de perte de qualité de vie. Pour tenir compte des éléments spécifiques à chaque pays, l'analyse s'est concentrée sur la population du Royaume-Uni, un pays qui dispose d'un grand nombre de sources de données sanitaires fiables. En supposant une relation de cause-à-effet entre la consommation de yaourt et une plus faible incidence du diabète, comme rapporté dans les publications scientifiques, les résultats de cette étude indiquent qu'une augmentation de la consommation de yaourt de 100 g par jour/personne dans la population adulte du Royaume-Uni pourrait générer des économies substantielles pour le système national de santé, ainsi qu'une amélioration significative de la qualité de vie de la population, en réduisant l'incidence du diabète de type 2.

Le **chapitre 9** traite d'un problème de santé qui touche même les personnes ayant un mode de vie sain et de bonnes habitudes alimentaires : les infections respiratoires saisonnières et les syndromes grippaux. Ces maladies virales sont courantes dans le monde entier et font peser une charge considérable sur les systèmes de santé nationaux, ainsi que sur les individus, les familles et la société dans son ensemble. Deux méta-analyses, publiées par la Cochrane Library et par le York Health Economics Consortium, ont confirmé l'effet bénéfique des probiotiques (bactéries vivantes qui ont un effet positif sur notre santé) pour réduire l'incidence et la durée de ces états grippaux; avec une réduction de l'utilisation d'antibiotiques et une diminution de l'absentéisme. Afin d'évaluer l'effet des probiotiques dans la prévention et la réduction des symptômes,

il est à nouveau crucial de prendre en compte les données spécifiques à chaque pays et la manière dont les soins de santé locaux sont organisés. Ainsi, ce chapitre est divisé en trois sections qui, sur la base d'un même modèle informatique, présentent les résultats socio-économiques pour respectivement la France, le Canada et les États-Unis. Outre le fait que ces analyses montrent des économies significatives pour chaque pays, quelles que soient les conditions d'assurance et d'arrêt maladie, cette série d'études confirme qu'il est possible d'adapter efficacement un modèle pilote soigneusement construit pour un pays donné - en l'occurrence la France - pour effectuer des évaluations nutritionnelles et économiques dans d'autres pays.

Pour conclure cette thèse, la première partie du **chapitre 10** décrit comment l'économie de la nutrition a progressivement gagné en reconnaissance depuis son introduction en 2011. Ce constat est fondé sur une analyse de la littérature scientifique pour la période janvier 2012-décembre 2021 et donne un aperçu de la variété des sujets d'étude publiés au cours de cette première décennie par des groupes de recherche indépendants ou autres parties prenantes. Dans la deuxième partie de ce chapitre, une perspective est esquissée pour le développement futur de l'économie de la nutrition au cours de la deuxième décennie de son existence. La prévalence sans cesse croissante des maladies chroniques causées par des facteurs de risque associés au comportement alimentaire quotidien et autres modes de vie menace la pérennité des systèmes de santé ainsi que la prospérité de la population générale et le bien-être des individus. Il est urgent de donner un tournant définitif à cette situation. Nous ne pouvons pas nous permettre de continuer à « manger » notre santé, avec comme résultat des demandes excessives (mais évitables) sur les ressources limitées des soins de santé ; surtout maintenant que la pandémie de COVID a exercé une pression sans précédent sur les structures et les établissements de santé.

Les changements de comportement dans l'activité physique et les habitudes alimentaires quotidiennes sont l'épine dorsale des politiques de prévention en matière de santé publique, mais leur mise en œuvre représente un énorme défi, comme en témoignent, par exemple, les difficultés de réduire la consommation d'alcool ou le tabagisme. Une collaboration plus systématique entre les chercheurs scientifiques et les volontaires du grand public, en coordination ou non avec les agences gouvernementales et autres acteurs, offre - à mon avis - une opportunité inégalée de mieux comprendre les facteurs subjectifs qui jouent un rôle clé dans le mode de vie et les habitudes alimentaires quotidiennes. De tels projets d'étude, basés sur la science citoyenne, sont encore assez rares dans le monde de l'alimentation, mais ils sont susceptibles de fournir un excellent levier pour obtenir un plus grand engagement au niveau de la population. En même temps, la participation active à ces projets motiverait les volontaires à évoquer spontanément

l'expérience dans leur propre environnement professionnel et personnel. Dans le climat actuel de méfiance à l'égard des recommandations gouvernementales d'une part, et, d'autre part la tendance d'un grand nombre de gens à prendre pour argent comptant des informations (non vérifiées et) non fondées sur Internet, l'interaction entre la science citoyenne et les projets d'évaluation nutritionnelle contribuera à une meilleure prise de conscience du rôle essentiel de l'alimentation quotidienne dans le bien-être personnel. Cela favorisera la volonté de changer durablement de comportement, ce qui à plus long terme profitera non seulement aux systèmes de santé, mais aussi aux conditions socio-économiques et à la population en général.

La littératie nutritionnelle est le début d'un monde plus sain et socialement plus équitable. Pour un vrai savoir vivre, sachons manger !

List of Publications

Coding Public Health Interventions for Health Technology Assessments: A Pilot Experience With WHO's International Classification of Health Interventions (ICHI). Wübbeler M, Geis S, Stojanovic J, Elliott, L Gutierrez-Ibarluzea I, Lenoir-Wijnkoop I**.** *Front Public Health. 2021 Jun 16;9:620637. doi:10.3389/fpubh.2021.620637. eCollection 2021*

Evaluating Public Health Interventions: A Neglected Area in Health Technology Assessment. Stojanovic J, Wübbeler M, Geis S, Reviriego E, Gutiérrez-Ibarluzea I, Lenoir-Wijnkoop I. *Front Public Health. 2020 Apr 22;8:106. doi:10.3389/fpubh.2020.00106. eCollection 2020*

Probiotics Reduce Health Care Cost and Societal Impact of Flu-Like Respiratory Tract Infections in the USA: An Economic Modeling Study. Lenoir-Wijnkoop I, Merenstein D, Korchagina D, Broholm C, Sanders ME, Tancredi D. *Front Pharmacol. 2019 Aug 28;10:980. doi:10.3389/fphar.2019.00980. eCollection 2019*

Medical Nutrition Terminology and Regulation in the United States and Europe: a Scoping Review. Freijer K, Volger S, Pitter JG, Molsen-David E, Clarissa Cooblall, MPH†, Evers S, PhD, Hiligsmann M, PhD, Aurelie Danel A, Partridge J, Goates S, PhD, Laplante S, Seyhun O, MSc, Aggarwal BD, Ofili T, Lenoir-Wijnkoop I. *Value Health. 2019 Jan;22(1):1-12. doi:10.1016/j.jval.2018.07.879.*

Does probiotic consumption reduce antibiotic utilization for common acute infections? A systematic review and meta-analysis. King S, Tancredi D, Lenoir-Wijnkoop I, Gould K, Vann H, Connors G, Sanders ME, Linder JA, Shane AL, Merenstein D. *European Journal of Public Health*, 2019 Jun 1;29(3):494-499. doi:10.1093/eurpub/cky185

The costs of functional gastrointestinal disorders and related signs and symptoms in infants: a systematic literature review and cost calculation for England. Mahon J, Lifschitz C, Ludwig T, Thapar N, Glanville J, Miqdady M, Saps M, Quak SH, Lenoir Wijnkoop I, Edwards M, Wood H, Szajewska H. *BMJ Open. 2017 Nov 14;7(11):e015594. doi:10.1136/bmjopen-2016-015594*

The potential of daily nutrition as preventative health technology. Lenoir-Wijnkoop I. *European Journal of Public Health, Volume 27, Issue suppl_3, 1 November 2017, ckx187.061, https://doi.org/10.1093/eurpub/ckx187.061*

The Clinical and Economic Impact of Probiotics Consumption on Respiratory Tract Infections: Projections for Canada. Lenoir-Wijnkoop I, Gerlier L, Roy D, Reid G. *PLoS One. 2016 Nov 10;11(11):e0166232. doi: 10.1371/journal.pone.0166232***.**

Costs associated with functional gastrointestinal disorders and related signs and symptoms in infants: a systematic review protocol. Glanville J, Ludwig T, Lifschitz C, Mahon J, Miqdady M, Saps M, Hock Quak S, Lenoir-Wijnkoop I, Edwards M, Wood H, Szajewska H. *BMJ Open. 2016 Aug 24;6(8):e011475. doi: 10.1136/bmjopen-2016-011475. Review. Erratum in: BMJ Open. 2016 Sep 09;6(9)***.**

Is consuming yoghurt associated with weight management outcomes? Results from a systematic review. Eales J, Lenoir-Wijnkoop I, King S, Wood H, Kok FJ, Shamir R, Prentice A, Edwards M, Glanville J, Atkinson RL. *Int J Obes (Lond). 2016 May;40(5):731-46. doi:10.1038/ijo.2015.202*.

An economic model for the use of yoghurt in type 2 diabetes risk reduction in the UK. Lenoir-Wijnkoop I, Mahon J, Claxton L, Wooding A, Prentice A, Finer N. **(**2016) *BMC Nutrition* 2, 77.

Editorial: Today's Nutrition and Tomorrow's Public Health: Challenges and Opportunities. Lenoir-Wijnkoop I, Gutiérrez-Ibarluzea I, Dubois DJ. *Front Pharmacol. 2016 Feb 24;7:34. doi: 10.3389/fphar.2016.00034.*

Metrics to analyze public health interventions that aim to impact on CVD prevention: a HTA perspective. Gutiérrez-Ibarluzea I, Dubois D, Lenoir-Wijnkoop I. *European Journal of Public Health, Volume 25, Issue suppl_3, 1 October 2015, ckv167.046, https://doi-org.proxy.library.uu.nl/10.1093/eurpub/ckv167.046*

Urinary tract infections: Economical impact of water intake. Bruyère F, Buendia-Jiménez I, Cosnefroy A, Lenoir-Wijnkoop I, Tack I, Molinier L, Daudon M, Nuijten MJ. *Prog Urol. 2015 Sep;25(10):590-7. doi: 10.1016/j.purol.2015.05.010*.

Health economic modeling to assess short-term costs of maternal overweight, gestational diabetes, and related macrosomia - a pilot evaluation. Lenoir-Wijnkoop I, van der Beek EM, Garssen J, Nuijten MJ, Uauy RD. *Front Pharmacol. 2015 May 20;6:103. doi: 10.3389/fphar.2015.00103*.

Public health and budget impact of probiotics on common respiratory tract infections: a modelling study. Lenoir-Wijnkoop I, Gerlier L, Bresson JL, Le Pen C, Berdeaux G. *Plos One. 2015 Apr 10;10(4):e0122765. doi:10.1371/journal.pone.0122765*.

Editorial: Public health interventions and nutrition as a preventative health technology. Lenoir-Wijnkoop I. *Int J Technol Assess Health Care. 2014 Oct;30(4):343-4. doi:10.1017/S0266462314000555*.

The view of European experts regarding health economics for medical nutrition in disease-related malnutrition. Freijer K, Lenoir-Wijnkoop I, Russell CA, Koopmanschap MA, Kruizenga HM, Lhachimi SK, Norman K, Nuijten MJ, Schols JM. Eur J Clin Nutr. 2015 May;69(5):539-45. doi: 10.1038/ejcn.2014.280. Epub 2015 Jan 21.

Nutrition Economics - An Introduction. Freijer K; Lenoir-Wijnkoop I; Nuijten MJC; Evers SMAA, Molsen, E. *ISPOR Connections, Vol. 20, No. 4, 01.01.2014, p. 10-11***.**

Nutrition economic evaluation of a probiotic in the prevention of antibiotic-associated diarrhea. Lenoir-Wijnkoop I, Nuijten MJ, Craig J, Butler CC. Front Pharmacol. 2014 Feb 17;5:13. doi: 10.3389/fphar.2014.00013.

Probiotics and prebiotics: prospects for public health and nutritional recommendations. Sanders ME, Lenoir-Wijnkoop I, Salminen S, Merenstein DJ, Gibson GR, Petschow BW, Nieuwdorp M, Tancredi DJ, Cifelli CJ, Jacques P, Pot B. Ann N Y Acad Sci. 2014 Feb;1309:19-29. doi: 10.1111/nyas.12377.

Effects of genetic, processing, or product formulation changes on efficacy and safety of probiotics. Sanders ME, Klaenhammer TR, Ouwehand AC, Pot B, Johansen E, Heimbach JT, Marco ML, Tennilä J, Ross RP, Franz C, Pagé N, Pridmore RD, Leyer G, Salminen S, Charbonneau D, Call E, Lenoir-Wijnkoop I. *Ann N Y Acad Sci. 2014 Feb;1309:1-18. doi:10.1111/nyas.12363*.

Monitoring immune modulation by nutrition in the general population: identifying and substantiating effects on human health. Albers R, Bourdet-Sicard R, Braun D, Calder PC, Herz U, Lambert C, Lenoir-Wijnkoop I, Méheust A, Ouwehand A, Phothirath P, Sako T, Salminen S, Siemensma A, van Loveren H, Sack U. *Br J Nutr. 2013 Aug;110 Suppl 2:S1-30. doi: 10.1017/S0007114513001505*.

Nutrition economics - food as an ally of public health. Lenoir-Wijnkoop I, Jones PJ, Uauy R, Segal L, Milner J. *Br J Nutr. 2013 Mar 14;109(5):777-84. doi: 10.1017/S0007114512005107*. (Awarded Paper of the Month by the Nutrition Society)

Health economics and nutrition: a review of published evidence. Gyles CL, Lenoir-Wijnkoop I, Carlberg JG, Senanayake V, Gutierrez-Ibarluzea I, Poley MJ, Dubois D, Jones PJ. *Nutr Rev. 2012 Dec;70(12):693-708. doi: 10.1111/j.1753-4887.2012.00514.x.*

Increased water intake as a prevention strategy for recurrent urolithiasis: major impact of compliance on cost-effectiveness. Lotan Y, Buendia Jiménez I, Lenoir-Wijnkoop I, Daudon M, Molinier L, Tack I, Nuijten MJ. J *Urol. 2013 Mar;189(3):935-9. doi: 10.1016/j.juro.2012.08.254*

Workshop Report: concepts and methods in the economics of nutrition--gateways to better economic evaluation of nutrition interventions. Lenoir-Wijnkoop I, Nuijten MJ, Gutiérrez-Ibarluzea I, Hutton J, Poley MJ, Segal L, Bresson JL, van Ganse E, Jones P, Moreno L, Salminen S, Dubois D. *Br J Nutr. 2012 Nov 14;108(9):1714-20. doi: 10.1017/S0007114512003704*

Dairy foods and osteoporosis: an example of assessing the health-economic impact of food products. Lötters FJ, Lenoir-Wijnkoop I, Fardellone P, Rizzoli R, Rocher E, Poley MJ. *Osteoporos Int. 2013 Jan;24(1):139-50. doi: 10.1007/s00198-012-1998-6.*

Primary prevention of nephrolithiasis is cost-effective for a national healthcare system. Lotan Y, Buendia Jiménez I, Lenoir-Wijnkoop I, Daudon M, Molinier L, Tack I, Nuijten MJ. *BJU Int. 2012 Dec;110(11 Pt C):E1060-7. doi: 10.1111/j.1464-410X.2012.11212.x.*

Nutrition economics: towards comprehensive understanding of the benefits of nutrition. Koponen A, Sandell M, Salminen S, Lenoir-Wijnkoop I. *Microb Ecol Health Dis. 2012 Jun 18;23. doi:10.3402/mehd.v23i0.18585*.

Nutrition economics: an innovative approach to informed public health management. Nuijten M, Lenoir-Wijnkoop I**.** *Eur J Pharmacol. 2011 Sep;668 Suppl 1:S133-7. doi:10.1016/j.ejphar.2011.07.010.*

Health claims substantiation for probiotic and prebiotic products. Sanders ME, Heimbach JT, Pot B, Tancredi DJ, Lenoir-Wijnkoop I, Lähteenmäki-Uutela A, Gueimonde M, Bañares S. *Gut Microbes. 2011 May-Jun;2(3):127-33.*

Cost-effectiveness model for a specific mixture of prebiotics in The Netherlands. Lenoir-Wijnkoop I, van Aalderen WMC, Boehm G, Klaassen D, Sprikkelman AB, Nuijten MJC. *Eur J Health Econ. 2012 Feb;13(1):101-10. doi: 10.1007/s10198-010-0289-4*.

Nutrition economics - characterising the economic and health impact of nutrition. Lenoir-Wijnkoop I, Dapoigny M, Dubois D, van Ganse E, Gutiérrez-Ibarluzea I, Hutton J, Jones P, Mittendorf T, Poley MJ, Salminen S, Nuijten MJ. *Br J Nutr. 2010 Aug 27:1-9.*

Guidance for substantiating the evidence for beneficial effects of probiotics: probiotics in chronic inflammatory bowel disease and the functional disorder irritable bowel syndrome. Haller D, Antoine JM, Bengmark S, Enck P, Rijkers GT, Lenoir-Wijnkoop I. *The Journal of nutrition 2010;140(3):690S-7S.*

Guidance for substantiating the evidence for beneficial effects of probiotics: current status and recommendations for future research. Rijkers GT, Bengmark S, Enck P, Haller D, Herz U, Kalliomaki M, Kudo S, Lenoir-Wijnkoop I, Mercenier A, Myllyluoma E, Rabot S, Rafter J, Szajewska H, Watzl B, Wells J, Wolvers D, Antoine J. *The Journal of nutrition 2010;140(3):671S-6S.*

Dietary prebiotics: current status and new definition. GR. Gibson, KP. Scott, RA. Rastall, KM. Tuohy, A. Hotchkiss, A.Dubert-Ferrandon, M. Gareau, EF. Murphy, D. Saulnier, G. Loh, S. Macfarlane, N. Delzenne, Y. Ringel, G. Kozianowski, R. Dickmann, I. Lenoir-Wijnkoop, C. Walker, R. Buddington. *IFIS Functional Foods Bulletin 2010; 7:1-19*.

Responsible exploitation of scientific data on pro- and prebiotics for consumer health. SSA Gutimpact position paper. *Food Science and Technology Bulletin 2008*

Probiotic and Prebiotic Influence Beyond the Intestinal Tract. I Lenoir-Wijnkoop, ME Sanders, MD Cabana, E Caglar, G Corthier, N Rayes, PhM. Sherman, HM Timmerman, M Vaneechoutte, J. Van Loo, DAW Wolvers. *Nutrition Reviews 2007;65 (11):469-89.*

Acute calcium assimilation from fresh or pasteurized yoghurt depending on the lactose digestibility status. Parra MD, Martínez de Morentin BE, Cobo JM, Lenoir-Wijnkoop I, Martínez JA. *J Am Coll Nutr. 2007 Jun;26(3):288-94.*

Assessment of the benefits of Live Yogurt: Methods and Markers for *in vivo* Studies of the Physiological Effects of Yogurt Ferments. Piaia M, Antoine JM, Mateos-Guardia JA, Leplingard A, Lenoir-Wijnkoop I. *Microbial Ecology in Health and Disease 2003; 15: 79-87.*

Lactose intolerance: analysis of underlying factors. Vonk RJ, Priebe MG, Koetse HA, Stellaard F, Lenoir-Wijnkoop I, Antoine JM, Zhong Y, Huang CY. *Eur J Clin Invest. 2003 Jan;33(1):70-5.*

15N as a marker to assess portal absorption of nitrogen from milk, yogurt and heat-treated yogurt in the growing pig. Rychen G, Mpassi D, Jurjanz S, Mertes M, Lenoir-Wijnkoop I, Antoine JM, Laurent F. *J Dairy Res. 2002 Feb;69(1):95-101.*

Portal absorption of 15N and amino nitrogen in the growing pig after ingestion of labelled milk, yogurt or heat-treated yogurt. Mpassi D, Rychen G, Feidt C, Mertes M, Laurent F, Lenoir-Wijnkoop I, Antoine JM. *Reprod Nutr Dev. 2001 Mar-Apr;41(2):153-62.*

The 13C/2H-glucose test for determination of small intestinal lactase activity. Vonk RJ, Stellaard F, Priebe MG, Koetse HA, Hagedoorn RE, De Bruijn S, Elzinga H, Lenoir-Wijnkoop I, Antoine JM. *Eur J Clin Invest. 2001 Mar;31(3):226-33.*

Relationship between lactose digestion, gastrointestinal transit time and symptoms in lactose malabsorbers after dairy consumption. Labayen I, Forga L, Gonzalez A, Lenoir-Wijnkoop I, Nutr R, Martinez JA. *Aliment Pharmacol Ther. 2001 Apr;15(4):543-9.*

Intestinal and colonic factors involved in lactose intolerance. RJ Vonk, MG Priebe, F Stellaard, H Elzinga, HA Koetse, Y Lin, C Huang, JM Antoine, I Lenoir-Wijnkoop. *Fed Am Soc Exp Biology 2000*

Immunity and probiotics*.* Dugas B, Mercenier A, Lenoir-Wijnkoop I, Arnaud C, Dugas N, Postaire E. *Immunol Today. 1999 Sep;20(9):387-90.*

Contribution du goûter aux apports nutritionnels d'enfants agés de 2ans, 6 ans et 10 ans. Deheeger M, Arnaud C, Lenoir-Wijnkoop I, Cachera M-FR *Cahiers de Nutrition et de diététique. 1999, vol 34, S1*

Other Publications, initiated and/or (co-)edited

Video Infographic: The power of nutrition economics. Irene Lenoir-Wijnkoop on behalf of the HTAi Interest Group on Public Health (2019). Accessible via: https://htai.org/blog/2019/01/02/the-power-of-nutrition-economics-an-infographic-from-inphorm/

E-book: Today's nutrition and tomorrow's public health: challenges and opportunities. Editors Irene Lenoir-Wijnkoop, Iñaki Gutiérrez-Ibarluzea, Dominique J Dubois. (2016) Published in Frontiers in Pharmacology Drugs Outcomes Research and Policies. Accessible via: Front. Pharmacol. doi: 10.3389/fphar.2016.00034

Educational DVD: So which bacteria did you eat today. Written and produced by Gregor Reid & Irene Lenoir-Wijnkoop. Translated and edited in 8 languages

Health Effects of Probiotics and Culture-Containing Dairy Products in Humans. Bulletin of the International Dairy Federation 380/2003

Eating Frequency and Health. Mougins 2003. Nutr & Health Collection, Ed. JLB Eurotext

The Intestinal Microflora, Understanding the Symbiosis. Paris 2003. Nutr & Health Collection, Ed. JLB Eurotext

Fermented Foods, Fermentation and Intestinal Flora. Eur J of Clin Nutr. 2002; 56: S1-S58

Fermented Foods and Healthy Digestive Functions. Mexico 2001. Nutr & Health Coll., Ed. JLB Eurotext

Glycaemic Index and Health: the Quality of the Evidence. Bandol 2001. Nutr & Health Coll., Ed. JLB Eurotext. Nutricion Clinica y Dietética Hospitalaria 2001; 21: 20-44. Ed. EMD Healthcare Communications CHINA 2003

Functional Dairy Products. New York 2000. Nutr & Health Coll., Ed. JLB Eurotext

Stress and Nutrition: a Fascinating Crosstalk. Ostwald, 2000. Nutr & Health Collection, Ed. JLB Eurotext

Nutrition and Successful Ageing. Biarritz 1999; Nutr & Health Coll., Ed. JLB Eurotext

Yoghurt: Eighty Years of Active Research for Health. Barcelona 1999; Nutr & Health Collection, Ed. JLB Eurotext

Immunity and Probiotics. Bonn 1998. Nutr & Health Collection, Ed. JLB Eurotext

Lipids from Alpha to Omega. Bordeaux 1998. Nutr & Health Collection, Ed. JLB Eurotext

Mechanisms of Protection of the Digestive Tract. Paris 1998; Nutr & Health Collection, Ed. JLB Eurotext

Patterns of food intake in schoolchildren. Saint-Paul-de-Vence 1997; IRVINN Editions

Acknowledgments
Dankwoord
Remerciements

It all started in 2005, when Dr Mary Ellen Sanders asked me if I had a suggestion for an original working session for the next annual conference of the International Scientific Association for Probiotics and Prebiotics (ISAPP). The result of these exchanges was a discussion group on 'probiotic and prebiotic influence on sites distant from the intestinal tract', an almost unexplored territory at that point in time. It allowed the speakers to address a great variety of innovative topics and for me it was the very first opportunity to present and discuss, in front of an international audience of fundamental researchers and clinical scientists, my intitial thoughts about the cost-saving potential of nutrition. Thank you so much Mary Ellen, it opened a new chapter in my career, which now reaches an important achievement. Through the years ISAPP has always been willing to consider proposals for an out-of-the-box topic related to Nutrition Economics and Public Health. I am extremely grateful for that.

I also wish to express my gratitude to Pr Seppo Salminen, who invited me in an early phase to address the topic of nutrition economics at the Functional Food Forum in Turku, who contributed to the expert meetings in Amsterdam and Bilbao, who came to the Dairy Summit in Parma to defend the concept Nutrition Economics and who continues to involve me in ongoing work. Dear Seppo, our discussions and co-writing activities have always been so pleasant. Many thanks for your continuing interest and for your kindness.

I should also mention Dr Mark Nuijten and Pr Dominique Dubois. Mark and Dominique, thank you for contributing to this field. Mark, thank you for your explanations about models. Our shared lectures on nutrition economics for the students of the École Doctorale, Université Diderot in Paris, were fun. Dominique after the consensus meetings we fought, together with Dr Iñaki Gutierrez Ibarluzea, for getting nutrition recognized as a health technology. I could always count on you and your unfailing knowledge in the area of quality-of-life. Iñaki, after our tremendous efforts during all those years, the many different initiatives and our relatively recent endeavour to position nutrition as a neglected health technology, I dearly hope that in the next few years we will witness a change of paradigm, shifting the focus from treatment & disease to health & prevention. The related uncertainties and hurdles will remain challenging and a source for further stimulating exchanges. I appreciate all you undertake within the HTAi society as well as in the field of health economics in general. Eskerrik asko!

The first time I contacted Dr Karen Freijer, an unknown colleague specialized in oral supplements and disease-related malnutrition, my objective was to discuss the feasibility and the necessary steps for creating nutrition economics as a new discipline. Our cooperation, in the beginning based on professionalism and mutual respect,

grew into a deep and long-lasting friendship. Lieve Karen, dank voor je inzet en je enthousiasme.

When the scientific part of this dissertation came to an end, I started to inform my personal environment about my intentions. It was wonderful to discover a different kind of support. First of all, the proudness of my kids who have themselves grown up to be extraordinary adults. Lieve Charlotte, Pierre et Sophie, je vous aime. C'est moi qui suis tellement fière de vous et de vos choix qui donnent un réel sens à la vie. Mille mercis! Petit Tony, mon super-héros, la couverture est magnifique, une vraie valeur ajoutée à cette thèse et au sens profond des messages que j'espère faire passer par ce travail. Bravo lieverd, en dank je wel pour ton beau dessin.

The warm presence from my siblings and good friends has been an unexpected gift. Koen, ik heb veel plezier gehad van het computerlampje dat je me een paar maanden geleden cadeau deed en waardoor ik dag en nacht (!) door kon werken. De interesse van Ute en jou is me heel dierbaar. Astrid en Liesbeth, fijn dat jullie bereid waren de Nederlandse samenvatting na te kijken op mijn wat roestige gebruik van onze moedertaal. En aan jullie allemaal, dank voor de gezellige uitwisselingen tijdens de afronding.

Agnès, c'est en grande partie grâce à toi que j'ai retrouvé le monde de la nutrition en quittant la pharma et les pathologies lourdes qui étaient mon quotidien. C'était un nouveau départ - il y 25 ans - qui n'aurait pas eu lieu sans tes talents de coach et ton grand sens de discernement. Notre amitié, qui s'est installée depuis, m'est très chère. Anouck & Philippe, Claire & Frédéric, un grand merci pour votre soutien et votre temps pendant la dernière ligne droite, plutôt mouvementée, de ce parcours. Et j'ai savouré vos louanges quant à ma maitrise de la langue de Molière.

It took a couple of years, a lot of energy and a strong personal belief to pioneer the field of nutrition economics, and I would never have succeeded without the kind support of many other fantastic people. Without citing each of them, I convey my heartfelt thanks to all the scientists and practitioners who took part in my study projects and cosigned the resulting papers; your name is indicated at the beginning of the relevant chapters. I feel honored that you agreed to contribute to my work.

Last but not least I would like to thank the members of the Assessment Committee and of course my promotors, Prs Johan Garssen and Eric Claassen. Eric, our paths crossed so many years ago, I don't even remember exactly when. In any case well before you wrote an editorial to accompany my publication on probiotics and antibiotic-associated diarrhea. Throughout the years it has always been a pleasure to talk with you, to

work with you and your positive energy is an example. Thank you for being one of my promotors.

Johan, all this would probably never have happened without you. Your trust and relentless enthusiasm were a real booster when I needed it. During this uncommon PhD route, I had to overcome quite some obstacles, fight incredulity or even opposition - you left me a total freedom in doing so and probably understood better than anyone else that this was the right way for me to reach the finish. You recently called me an unorthodox PhD candidate, but you sure are a most unorthodox promotor. En nu is het zover. Reuze bedankt Johan, voor jouw aandeel in dit welslagen.

About the author

After obtaining her gymnasium-ß diploma in 1972 at the Baarnsch Lyceum, Irene Lenoir-Wijnkoop studied Nutrition and Dietetics at the Professor Kohnstamm Academy in Amsterdam. After her graduation, she started her career in the cancer clinic where she quickly became interested in the interactions between nutrition and chemotherapy. In 1979 this led to an appointment at Upjohn Nederland, a pharmaceutical company that at the time offered the opportunity to pursue an additional study in the field of pharmacology, pharmacokinetics and pharmacodynamics.

After her marriage to a Frenchman in 1983, Upjohn agreed to keep Irene on as an employee of the French branch, where she worked as Medical Science Liaison officer in the field of blood cancer and HIV infections. Diseases that were often accompanied by symptoms such as cachexia. and wasting syndrome, which in a way brought her back to nutrition. In 1997, after a long experience with heavy pathologies, she decided it was time to turn to the brighter side of health, and she joined the R&D department of Danone, a French multinational food-products corporation, where she initiated the clinical research activity in the field of fermented dairy products and health. Over the following years, she successively created the scientific communication department and managed the international scientific network. She also served on many advisory boards and committees, both in France and internationally. Her affiliation with Utrecht University started during the autumn 2012. Six years later, in 2018, she decided to turn her back for good on her employment with Danone and its inevitably associated marketing practices.

In addition to her activity with the Utrecht University, Irene is now established as an international consultant in the field of Public Health Nutrition.