TODAY'S NUTRITION AND TOMORROW'S PUBLIC HEALTH: CHALLENGES AND OPPORTUNITIES

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TODAY'S NUTRITION AND TOMORROW'S PUBLIC HEALTH: CHALLENGES AND OPPORTUNITIES

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Daily alimentation has a major influence on the lifetime health status of any citizen in the world and appropriate approaches for determining the impact of small food effects on the long term represent an essential guiding light in the search for sustainable health solutions
Image taken from: https://pixabay.com/en/lighthouse-ocean-sea-light-coast-980457/

At the dawn of the third millennium, we are confronted with a disturbing phenomenon: although global life expectancy still increases, this is not the case for healthy life expectancy! The explanation of this seemingly contradiction is mainly due to the rising prevalence of the new pandemia of chronic non-communicable diseases (NCDs). Even in low and middle income countries, the improvement in healthcare status and life expectancy is paralled by the increase of NCDs, as in all countries worldwide. Since the United Nations General Assembly held in New York in 2011, many publications have emphasized the close link between NCDs and nutrition.

The NCDs epidemic forces us to reconsider the public health perspectives. Many governments, non-governmental organizations and other institutions are actively involved in educational nutrition programs and campaigns; however their efforts seldom obtain the results hoped for. It is extremely difficult to induce changes in lifestyle and behavior that have built up over a long period of time. However, it becomes urgent to adapt to our changing life-environment where traditional wisdom and intuitive choices are giving way to individual thinking and search for (often uncontrolled) information.

This engenders a number of unprecedented challenges and it calls for a re-appraisal of the existing paradigms to achieve an adequate management of the upstream determinants of health instead of a (pre)dominant medical and hospital-centric approach. In the era of personalized healthcare, it is time to empower policy makers, professionals and citizens for achieving an evidence-based change in the health-disease interface and decision-making process for public health interventions.

The scientific and professional society Health Technology Assessment International (HTAi) has recognized nutrition as a health technology by creating a Interest Group (IG) dedicated to research on methodologies and assessments of nutrition-related public health, while taking into account contextual factors (ethical, legal, social, organizational, economic, …) in order to generate meaningful outcomes for establishing evidence-based health policies.

This Research Topic aims to elaborate on some of the potential hurdles which have to be overcome for the sake of sustainable healthcare provisions anywhere in the world, such as shortcomings in methodological approaches, regulatory frameworks, gaps between evidence, its hierarchy and final recommendations for public health management.

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EDITORIAL
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Editorial: Today's Nutrition and Tomorrow's Public Health: Challenges and Opportunities

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The Editorial on the Research Topic

Today's Nutrition and Tomorrow's Public Health: Challenges and Opportunities

Scientific research in the field of nutrition and health has made great strides in recent years. Food-related investigations cover a broad range of topics in close relation with many other health-oriented disciplines. This E-book elaborates on the relevance of putting diet and food habits at the heart of strategies aiming to improve the global health status of the general public, and on the need of appropriate methodological approaches to conduct meaningful and reliable public health- and economic outcome evaluations.

An emerging issue in the field of nutrition is the important role of our food on physiological homeostasis and resilience of the human body, as highlighted by Tremblay et al. The authors shed a new light on the obesity issue by addressing various functionalities of the adipose tissue, looking beyond its traditional function of excess energy storage. The multifactorial interplay between biological, environmental, and socioeconomic determinants may provide a plausible explanation of the obesity epidemics. The documented examples include:

- short sleep duration as a predictive variable for weigh gain
- the shift from physical work to cognitive efforts leading to a decreased energy expenditure but an increased energy intake, possibly due to an impaired satiation process
- uptake of chemical pollutants by the adipose tissue, which allows protection of other body tissues, but seems associated with a higher risk to develop a metabolic syndrome.

Further, research on the involvement of the adipose tissue in many regulatory processes will allow to better understand how nutrition-related body homeostasis should be taken into account in relation to the global constraints of sustainable development.

Another environmental key player is the microbiome ecosystem, an integrated part of the human organism. Ganesh and Versalovic present an insightful review on the role of our gut microbiota, and its composition, on health and disease. On the basis of a careful review of the literature with a focus on immune regulation, the authors address the direct and indirect interplay between the gastro-intestinal tract, its commensals and nutrients, both ingested and produced through metabolic processes. Bacterial-derived metabolites are known to influence host immune responses, while dysregulation of the related cellular and molecular pathways may affect the gut functionalities and increase the host's susceptibility to immune-mediated pathologies. This underlines the importance of beneficial micro-organisms in regulating the homeostasis of the human body. Further, investigations of these mediating properties can have important implications

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for the development of cost-effective preventative interventions to manage the increasing number of gastro-intestinal and metabolic disorders.

When studying the effects of food on human beings in their macro- or micro-environment, the citizen him- or herself—whether considered as being healthy, part of an at risk population or a patient—is obviously an "interfering" factor who impacts the larger public health context. Based on these considerations, Segal and Opie make a strong plea for implementing comprehensive nutrition strategies to reduce the diet-related disease burden. Such strategies need to incorporate both public health approaches and expanded publicly funded dietetic services. Multi-component strategies are proposed which include social marketing, regulatory restrictions on advertising of junk food/drinks, punitive taxes on unhealthy foods, suitable food labeling and publicly funded dietician services. Dietetic services are suggested to be part of core health service delivery and funded at a level that supports access to individualized dietetic services. Adopting such strategies may lead to substantial improvements in diet quality, better health, and wellbeing and lower healthcare costs.

A similar line of thought can be found in the work by Lenoir-Wijnkoop et al. who propose a health economic framework to assess short-term costs of maternal overweight, gestational diabetes, and related macrosomia. The authors point out that, in spite of the indubitable impact of overweight and obesity on public health, not much focus has been put on their social and economic consequences. The calculation of the costs associated to maternal overweight, gestational diabetes, and related macrosomia indicated that health expenditures are considerable. In fact, the conservative estimation of the decision analytical techniques based model, using US costing data, provided an annual cost close to 2 billion US$. These results underpin the hypothesis that public health interventions devoted to lifestyle, diet, and physical activity not only improve health status, but also have measurable social and economic consequences. The long-term potential of these interventions should be considered in the prevention of non-communicable diseases and healthcare systems sustainability.

An important element that might help to improve the efficacy of the above mentioned nutrition strategies and interventions, is introduced by Ruano-Rodríguez et al. They discuss the increasing need for "customer" self-reported outcome measures of Health-Related Quality of Life (HRQoL) in the field of nutrition, including unhealthy lifestyles and dietary habits. A literature research revealed that the generic SF-36® is the most frequently used health status questionnaire. However, very few validated HRQoL measurement instruments are available to address the specific context of preventative dietary interventions. Contextual diet-specific HRQoL measures are needed for evaluating the impact of diet habits on daily life functioning and wellbeing.

Context is indeed key for obtaining meaningful research outcomes on nutrition and health. Therefore, future progress in this area will also depend on our ability to integrate the nutritional dimension in a societal perspective as brought up by Poley. He addresses the challenges, opportunities of health technology assessment (HTA) in the field of nutrition interventions and its role in policy making. Nutrition and HTA used to be two worlds apart. However, consensus is growing that HTA can provide useful tools to substantiate the positive impact of nutrition on public health, despite the differences with HTA of disease treatment. For example, food products are typically paid "out-of-pocket" by the consumer rather than by a third-party payer. Contextual research should be able to address the methodological issues. In addition, better understanding of the policymakers' needs and efficient integration of HTA results into policy making will also be needed.

This idea is supported by Gutiérrez-Ibarluzea and Arana-Arri who revise the status of nutrition and its assessment by HTA specialists. Although HTA has an extensive scope and a wide range of technologies that could be considered under its remit, HTA has classically focused on the evaluation of medicinal products, medical devices, and their consequences for the healthcare systems. This overview shows that HTA specialists, mainly from high income countries, are increasingly interested in evaluating nutrition and its consequences. Well-established institutions have even suggested methodological approaches to the assessment of nutrition and have reported the utility of systematic reviews and economic evaluations to address the impact of nutrition. That notwithstanding, the evaluation of nutrition, as is the case of other public health interventions, requires the refinement of some commonly used measures and standards, such as the Quality Adjusted Life Years (QALY) paradigm for economic evaluations.

Two other studies illustrate how traditional and widely consumed foodstuffs can have a considerable influence on daily health and nutrition-related public health issues. Abdullah et al. performed an economic evaluation on the potential cost-savings to the Canadian healthcare system of two diet related diseases, type 2 diabetes (T2D) and cardiovascular disease (CVD), by increasing the intake of dietary fiber by adults. The authors performed a three-step cost-of-illness analysis to identify the percentage of individuals expected to increase their fiber intake, the potential reduction rates of T2D and CVD and the related annual savings due to this reduction. The study findings show that 1 g increase per day in universal fiber consumption would result in annual cost-savings of up to 51 million CAD$ for T2D and 92 million CAD$ for CVD. Even in the most pessimistic scenario the cost-savings remained substantial. This study shows that strategies aiming to improve dietary fiber intake as part of a healthy diet could have a significant direct impact on healthcare and related costs.

And last but not least, Glanville et al. describe the outcomes of a scoping review of the volume of available evidence on the health effects of conventional yogurt consumption. Studies considered eligible for the scoping review were epidemiological studies, cohort studies, open label studies, and randomized controlled trials (RCTs). Two hundred and thirteen studies were identified as relevant to the scoping question. The review identified a number of outcomes for which there exists substantial primary evidence that may be suitable for systematic review and potentially meta-analysis.

The 103 pages of "Supplementary Materials" contain a wealth of information on the "Full Search Strategies" and summary tables on study outcomes in bone health, weight management, metabolic health, cardiovascular health, gastrointestinal health, cancer, diabetes, and other diseases. The Supplementary Tables for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fphar.2015.00246.

In summary, this Research Topic of Frontiers underlines the strong intertwinement of nutrition research with other scientific, social, economic, and political research fields. The real-world setting further adds to the complexity due to the central place of the citizen who appears to be an active, although often unconscious, influencer of his surroundings. Concerted efforts by all parties involved will be mandatory to obtain stronger evidence-informed insights to guide decisions on convincing strategies for efficient and sustainable changes in dietary habits and nutrition-related lifestyle. There is a lot at stake!

AUTHOR CONTRIBUTIONS

The two co-authors of this editorial, DD and IG, provided each part of the short summaries that refer to the full paper contributions received and published in this RT. When I had written the overall Editorial DD reread the proposed text which we then validated together before I finalized the document.

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PERSPECTIVE
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Adipose tissue and sustainable development: a connection that needs protection

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Obesity is generally considered as an excess body fat that increases the risk to develop ergonomic, metabolic, and psychosocial problems. As suggested in this paper, body fat gain is also a protective adaptation that prevents body lipotoxicity, contributes to the secretion of molecules involved in metabolic regulation, and dilutes lipid soluble persistent organic pollutants. Recent literature shows that this protective role of adipose tissue is more solicited in a modern context in which unsuspected factors can affect energy balance to a much greater extent than what is generally perceived by health care professionals. These factors include short sleep duration, demanding mental work, and chemical pollution whose impact is more detectable in a context dominated by economic productivity and competitiveness. Since these factors might also include the increase in atmospheric CO_2, it is likely that obesity prevention will need the support of a promotion in sustainable development, whether it is for human health, and well-being or global ecological protection.

Keywords: energy balance, obesity, sleep, pollution, mental work

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Obesity involves a wide and interactive range of genetic, biological, behavioral, and societal factors contributing to variations in its prevalence. The first law of thermodynamics provides a simple definition of obesity which is the result of an excess in energy intake over expenditure leading to an increase in stored energy as body fat. This increase in body fatness is associated with numerous adverse effects which impact body functionality and the ability to accomplish daily activities. This inconvenience includes ergonomic problems which affect gait, posture and displacement and increase the risk of falls and injuries. The obese individual is also frequently less metabolically healthy with the consequence and likelihood of developing diseases such as diabetes, CVD, and sleep apnea. Finally, excess body fat contributes to suboptimal feeding behaviors and sociopsychological traits that exert a negative influence on health and well-being.

Traditionally, the treatment of obesity and related complications has strictly focused on the first law of thermodynamics since low and very low calorie diets that were commonly prescribed were based on simple diet adjustments to achieve a negative energy balance. This restrictive approach was not inappropriate but failed to consider the body's biology underlying the matching between energy intake and expenditure. In practical terms, the inevitable outcome has been body weight regain in a context where regulatory processes could not sufficiently adapt to the long-term consequences of caloric restriction.

Today, excess body fat is considered more as a complex problem reflecting the difficulty of the body to be in harmony with its environment. This suboptimal body-environment interaction is partly attributable to unsuspected factors linked to the present

socioeconomic context that solicits body fat gain as a protective adaptation.

The main function of adipose tissue is probably to store lipids along with its remarkable endocrine role as revealed by the ever increasing number of immuno-metabolic factors that are found to be released by fat cells (Bluher and Mantzoros, 2015). Lipid storage can accommodate a quasi unlimited positive lipid balance due to the potential hypertrophy and hyperplasia of fat cells. In the obese individuals supervised in our previous weight-reducing interventions, the theoretical excess body fat is about 20 kg in both men and women, as shown in Supplementary Table S1. In addition, the estimates presented in this table suggest that these obese individuals should lose about half of their body fat to reach the theoretical threshold of a healthy body weight.

The clinical experience of our research team includes repeated attempts to promote a body weight loss in obese individuals that could "normalize" body weight and fat. In some of our studies, food habits and physical activity practices were modified and monitored to favor a negative energy balance to the point of resistance to further lose body fat (Tremblay et al., 1991; Doucet et al., 1999; Chaput et al., 2005). Although the outcomes were beneficial, we have never been able to induce morphological changes approaching the baseline theoretical target. Interestingly, the achievement of a threshold of resistance to further lose fat was accompanied by a significant increase in appetite sensations (Doucet et al., 2000a), a greater than predicted decrease in energy expenditure and leptinemia (Doucet et al., 2000b; Tremblay and Chaput, 2009), and a more pronounced trend toward hypoglycemia (Tremblay et al., 1999). These changes are concordant with the results obtained by other investigators in the same research context (Leibel et al., 1995; Rosenbaum et al., 2005). Globally, these observations raise the possibility that some protective functions of adipose tissue may underlie the resistance to lose fat to "normality" in individuals prone to obesity.

Is Obesity Adequately Perceived?

As indicated above, the main role that has been traditionally attributed to adipose tissue is the storage of excess energy/lipid. This effect is important since it protects non-adipose organs from the lipotoxicity that would necessarily occur when fat intake exceeds fat oxidation. The quantitative aspects of the role of fat storage in the context of overfeeding were evaluated in the Quebec twin overfeeding study in which an excess in energy intake was imposed over 100 days to young adult male twins (Tremblay et al., 1992). As shown in **Table 1**, the energy equivalent of fat gain (210 MJ) corresponded to about 60% of the excess energy intake. This result also emphasized that under conditions of substantial overfeeding, fat storage can explain a greater proportion of the disposal of excess energy/lipid intake compared to thermogenesis.

The discovery of leptin, Zhang et al. (1994) has confirmed the key role of adipose tissue in some regulatory processes underlying energy metabolism. Although the lipostatic theory of appetite control was proposed as early as the 1950s (Kennedy, 1953), no adipose tissue-related messenger with the potential to transmit a satiating signal had been subsequently identified up until this discovery. Following its identification and initial characterization, leptin was found to promote a reduction in body weight, and food intake (Pelleymounter et al., 1995). It was also found to be increased in obese people (Considine et al., 1996), suggesting a state of leptin resistance in individuals prone to obesity. In response to a weight-reducing program, an early decrease in leptin was observed and found to be related to the greater than predicted decrease in energy expenditure (Doucet et al., 2000b). The definitive proof of involvement of leptin in the metabolic response to weight loss was provided by the group of Leibel and Rosenbaum (Rosenbaum et al., 2005) when they partly restored baseline energy expenditure and sympathetic nervous system activity with the administration of leptin in the weight-reduced obese state.

TABLE 1 | Estimated mean energy balance in men subjected to 100 days of overfeeding.

	MJ
Excess energy intake	353
Body energy gain	
• Fat	210
• Fat-free mass	12
Estimated increase in energy expenditure	110
Unexplained energy expenditure	31

Adapted from Tremblay et al. (1992).

The leptin discovery has been followed by the identification of other bioactive factors produced by fat cells such as resistin (Steppan et al., 2001) and adiponectin (Yamauchi et al., 2001) which also exert a significant impact on energy metabolism and related variables. Today, the potential of adipose tissue to secrete numerous molecules involved in immuno-metabolic regulation is well recognized. This also highlights the capacity of adipose tissue to contribute to body homeostasis via its secretory potential.

Adipose tissue can also support body homeostasis via the uptake and dilution of lipid soluble compounds classified as persistent organic pollutants (POPs). These compounds are man-made chemical products which include high-performance, low-cost insecticides which are still present in the body of every individual on the planet despite their withdrawal from agricultural use in many countries several decades ago. Their persistence is partly explained by their long half-life and because they can be transported in the air from countries where they are still used toward cold areas of the planet (Ma et al., 2003). Several years ago, Lee et al. (2007) examined the association between five subclasses of POPs and metabolic health and found that organochlorine (OC) pesticides were strongly and consistently related to the development of the metabolic syndrome. Specifically, the odds ratio of displaying the syndrome was more than five times greater in the quartile of more polluted individuals compared to the lower quartile of study participants. As described in the next section of this paper, the management of body levels of POPs may become problematic in the context of a weight-reducing program.

In summary, scientific evidence shows that adipose tissue is not only a body storage compartment of excess energy/lipid intake but is involved in regulatory processes and also attenuates the exposure of target organs to body pollutants. As further discussed, this protective role of adipose tissue seems to be even more essential in a world where economic preoccupations dominate human development.

About Unsuspected Determinants of Obesity

According to the World Health Organization (2000), obesity has reached an epidemic state which has stimulated numerous public health agencies to develop programs aiming at the promotion of healthy body weight. In general, these programs have been based on healthy eating and an active lifestyle and have targeted people in all age categories. Despite these significant efforts, the prevalence of obesity has not decreased and has even increased (Flegal et al., 2010). Interestingly, this observation echoes the results of Klimentidis et al. (2011) who examined the profile of over 20,000 animals representing eight species living with or around humans in industrialized countries. It was found that average mid-life body weights have risen among primates and rodents living in research colonies, as well as among feral rodents and domestic dogs and cats. On the basis of these results, the investigators suggested "the intriguing possibility that the etiology of increasing body weights may involve several as-of-yet unidentified and/or poorly understood factors" (Klimentidis et al., 2011). This is concordant with our recent research experience demonstrating that non-caloric and non-traditional factors may have a better predictive capacity of the risk of overweight compared to participation in physical activity and diet macronutrient composition (Chaput et al., 2009). In the present paper, we describe the potential impact of some of these factors which are representative of the features of our modern lifestyle.

Sleep Duration and Quality

As early as the 1990s, epidemiological data documented the existence of a possible relationship between habitual short sleep duration and the proneness to overweight (Locard et al., 1992). Further laboratory standardized testing has confirmed the validity of this association. For instance, an experimentally controlled restricted sleep duration was shown to acutely decrease leptinemia and increase plasma ghrelin and cortisol concentrations and desire to eat (Spiegel et al., 1999, 2004). Further investigations demonstrated that short sleep duration induced a substantial increase in energy intake (Nedeltcheva et al., 2009; Brondel et al., 2010) and a decrease in spontaneous physical activity (Schmid et al., 2009). Accordingly, reduction in sleep was found to interfere with the ability to comply with a negative energy balance (Nedeltcheva et al., 2010).

Our previous population studies and clinical interventions are in agreement with these results. In the *Quebec en Forme* Project (Chaput et al., 2006), we observed that short sleep duration was a much better predictive variable of the risk for overweight compared to physical inactivity. Moreover, as shown in **Table 2**, the Quebec Family Study (QFS) showed that short sleep duration was more associated with the risk of overweight compared to a high-fat diet and lack of participation in vigorous physical activity (Chaput et al., 2009).

The QFS also showed that short sleepers who become good sleepers attenuate their increase in body fat over time (Chaput et al., 2012). From a mechanistic standpoint, this study confirmed that short sleep duration is related to reduced leptinemia (Chaput et al., 2007b) and to a greater susceptibility to hypoglycemia (Chaput et al., 2007a). Finally, our clinical experience confirmed the findings of Nedeltcheva et al. (2010) regarding the reduced ability of short sleepers to benefit from a weight-reducing program (Chaput and Tremblay, 2012). The latter study also demonstrated that a decrease in habitual sleep quality is related to a reduced response of body weight and fat to a weight loss program.

The relevance of these observations to the current socioeconomic context is certainly reinforced by the statistics of the US National Sleep Foundation that reports a decrease of 1.5–2.0 h of sleep since 1960 (Leproult and Van Cauter, 2010). This decrease in sleep time is not clearly understood but partly explained by our 24 h turbulent environment imposing awakeness and vigilance whether it is for social relationships or labor requirements. This reality also favors the emergence of a dilemma that is well exemplified by the control of plasma leptin levels. On one hand, there is the social pressure promoting short sleep duration which leads to reduced leptinemia. On the other hand, there are the body's regulatory processes that include body fat gain and its related increase in plasma leptin levels to permit body homeostasis.

Demanding Mental Work

Industrialization and computerization have promoted a progressive change in the nature of labor in most sectors of economic activity. Specifically, this shift has partly replaced somatic effort relying on muscle by mental work that depends on neuronal activity. From a metabolic standpoint, neurons have less metabolic flexibility than myocytes since they essentially rely on glucose to support their work. This has incited us to

TABLE 2 | Risk factors for overweight in adulthood: the Quebec Family Study (QFS).

Risk factors	Adjusted OR (Cross-sectional)	Additional weight gain vs. a reference group (kg) (6 years follow-up)
Short sleep duration	3.81*	1.65
High disinhibition eating behavior	3.8*	1.46
Non-participation in high-intensity physical exercise	2.03*	1.23
High dietary lipid intake	1.64**	0.61
High alcohol intake	1.37**	0.39

*$p < 0.01$, **$p < 0.05$.
Adapted from Chaput et al. (2007b).

examine the impact of mental work on glycemic stability. Our preliminary study (Tremblay and Therrien, 2006) as well as a subsequent investigation (Chaput et al., 2008) demonstrated that demanding mental work accentuates glycemia instability, including the proneness to mild hypoglycemia known to trigger episodes of food intake (Mayer, 1953; Louis-Sylvestre and Le Magnen, 1980).

The study of the acute effects of demanding mental work confirmed the potential of cognitive effort to promote hyperphagia. In a study first conducted at Laval University in female students (Chaput and Tremblay, 2007), a computerized reading-writing task was found to increase *ad libitum* energy intake by 229 kcal during a buffet-type meal served immediately after the task. Interestingly, the mental work session did not induce quantitatively important changes in energy expenditure compared to a relaxing task control. Furthermore, the increase in energy intake happened without a significant increase in feelings of hunger, suggesting that demanding mental work may impair the satiation process leading to the interruption of feeding.

A second study also performed at Laval University in female students showed that computerized tasks increased subsequent energy intake by 200–250 kcal (Chaput et al., 2008). The results of this study also revealed that the increase in glycemia instability, cortisol, and subsequent energy intake was more pronounced in women for whom the mental task was more demanding (Chaput and Tremblay, 2009a,b). This is in agreement with the recent demonstration that performing homework, perceived as stressful by male students is associated with an increase in total and abdominal fat (Michaud et al., 2015).

Chaput et al. (2011) extended the investigation of the effects of mental work to the study of video game sessions. As expected, energy expenditure was slightly increased by video game playing. However, this increase was much lower than the global impact of the session on subsequent energy intake resulting in a substantial positive energy balance.

As for sleep habits, the increase in school-related activities is a strong societal trend compared to sports and television viewing, as documented by Sturm (2005). Children are more and more fueled by the proliferation of new technologies (such as portable internet small devices) and they are now consuming media for the amount of time that most adults spend at work. It has been shown that the presence of a small screen in the sleep environment and screen time were associated with perceived insufficient rest or sleep (Falbe et al., 2015). The contribution of sleep to screen time's impact on obesity should be considered in future studies. Since performing exercise between a mental work session and a meal prevents positive energy balance (Lemay et al., 2014), it seems relevant to increase participation in physical activity to better balance mental and somatic stimulations whether at school or in work facilities. Although this scenario seems reasonable and justified, it is certainly relevant to emphasize that its potential implementation does not benefit from solid traditions in the industrialized world. In this regard, one of the most relevant examples is the habitual template of items in the negotiation of a working contract between directors of companies and unions of workers that very rarely consider this issue as a priority.

Chemical Pollution

The case of the disposal of lipid soluble OC compounds represents one of the key examples of the conflict that may oppose economic development and the promotion of human health and well-being. As indicated above, this becomes particularly obvious in the context of a weight-reducing program which decreases the dilution space of the pollutants. In obese individuals who are known to display a greater OC body load than lean controls (Pelletier et al., 2002a), a substantial fat loss has been repeatedly shown to increase plasma (Backman and Kolmodin-Hedman, 1978; Walford et al., 1999; Chevrier et al., 2000), and adipose tissue OC levels (Chevrier et al., 2000). Since this hyperconcentration occurs in a uniform way in every lipid compartment of the body (Pelletier et al., 2003), body fat loss increases the exposure of every target organ to the detrimental effects of these pollutants as a result. In the skeletal muscle, the fat loss-induced changes in some circulating pollutants were related to a greater decrease in skeletal oxidative enzymes than that predicted by body weight loss (Imbeault et al., 2002). Accordingly, we also observed that weight loss promoted a greater than predicted decrease in plasma thyroid hormone (T3) concentrations and resting metabolic rate in obese individuals (Pelletier et al., 2002b). Furthermore, when compared to plasma leptin as a predictor of weight loss-induced changes in sleep metabolic rate, changes in plasma OCs were more associated with those in energy expenditure (Tremblay et al., 2004). In summary, fat loss is associated with metabolic changes that negatively alter the control of energy expenditure in association with the enhancing effect on blood and tissue levels of lipid soluble POPs.

These results also raise the question of the possibility of taking advantage of a fat loss program to develop strategies aimed at the elimination of body OCs. This has been tested by Geusau et al. (1999) who strongly increased the clearance of tetrachlorodibenzodioxin (TCDD) with a supplementation of Olestra chips for 38 days in two individuals highly contaminated by 2, 3, 7, 8-TCDD. This is concordant with data reported by Moser and McLachlan (1999) who found an increase in the excretion of OCs induced by Olestra. In a severely contaminated individual, Redgrave et al. (2005) also observed a considerable decrease in OC concentrations after Olestra supplementation. In a more recent study, we found that the partial replacement of dietary lipids by Olestra in obese individuals subjected to a low-fat diet resulted in a decrease in plasma βHCH which was in contrast to the increase induced by the standard low-fat diet. However, we were unable to detect the same benefit for 18 other compounds of the OC category. From a mechanistic standpoint, Geusau et al. (1999) proposed that the non-absorbable nature of Olestra and its structure analog to lipids accentuates the OC gradient toward the gut and a resulting increase in fecal loss.

The OC profile of sea lions also provides useful information about the ability of adipose tissue to detoxify the body. For instance, Ylitalo et al. (2005) reported a negative relationship between blubber thickness and polychlorinated biphenyls (PCBs). This study also revealed that a low level of blubber fat is related to increased likelihood of carcinomas. The latter observation may also highlight that the ability of adipose tissue

to dilute POPs and to protect organs playing a key role in the body's viability is not unlimited.

Adipose Tissue and Sustainable Development

Chemical pollution is not the only environmental factor that may solicit the homeostatic protection of adipose tissue. Recent evidence suggests that atmospheric CO_2 can increase energy intake and thus promote a positive energy balance. According to Hersoug et al. (2012), an increase in atmospheric CO_2 slightly decreases the pH of body fluids which may be related to an increase in energy intake. These investigators also reported preliminary data reinforcing the idea that a small increase in atmospheric CO_2 in humans favors a positive energy balance. This is in agreement with evidence documenting a link between CO_2 and the control of hypothalamic orexin neurons (Williams et al., 2007). These observations obviously deserve confirmation which may reinforce the idea that the management of sustainable development should consider body homeostasis, particularly the solicitation of the protective role of adipose tissue.

Conclusion

The management of obesity is generally performed via the promotion of healthy eating and an active lifestyle together with adequate psychosocial support. Although such a paradigm is sound and justified, we argue in this paper that the prevention of excess body fat also deserves the promotion of sustainable development. This vision is based on the consideration of the protective role of adipose tissue on body homeostasis which, beyond excess lipid storage, secretes molecules that are essential to some regulatory processes. In addition, adipose tissue plays a key role in body detoxification mostly via the dilution of lipid soluble POPs. In this context, the main idea for obesity prevention has some resemblance with that underlying the promotion of a healthy planet (i.e., not to oversolicit the protective resources of the host). As explained in this paper, this is difficult to manage in a modern world where daily socioeconomic requirements impose to the body (adipose tissue) some non-traditional demands that likely exert a strong adipogenic impact. Furthermore, by considering the rise in atmospheric CO_2 as a potentially obesogenic factor, it is likely that the foreseeable future might be worse than what we currently experience in terms of the obesity epidemic. In fact, it appears that no significant progress regarding obesity management and sustainable development will be achieved as long as money-making preoccupations will continue to dominate those related to human development. More research, and particularly multifactorial research, is needed to investigate the environmental and socioeconomic determinants of obesity. Experimental studies are also necessary to better understand the impact of environmental determinants such as pollutants on the regulation of energy metabolism. Globally, this research should permit a better understanding of the interaction between biological and lifestyle factors and their impact on the proneness to obesity.

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Supplementary Material

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fphar.2015.00110/abstract

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REVIEW
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Luminal Conversion and Immunoregulation by Probiotics

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Beneficial microbes are responsible for the synthesis of nutrients and metabolites that are likely important for the maintenance of mammalian health. Many nutrients and metabolites derived from the gut microbiota by luminal conversion have been implicated in the development, homeostasis and function of innate and adaptive immunity. These factors clearly suggest that intestinal microbiota may influence host immunity via microbial metabolite-dependent mechanisms. We describe how intestinal microbes including probiotics generate microbial metabolites that modulate mucosal and systemic immunity.

Keywords: probiotics, metabolites, commensal bacteria, immunomodulation, diet, dietary compounds, microbiome

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INTRODUCTION

The mammalian gastrointestinal tract, site for digestion and nutrition absorption harbors commensal microbiota, a population composed of 1000–5000 different bacterial species. Metagenomics of the Human Intestinal Tract (MetaHit) project containing 249 newly sequenced samples with 1,018 previously sequenced samples were combined to create a cohort from three continents. From this the integrated gene catalog (IGC) comprising 9,879,896 genes were established. The catalog includes close-to-complete sets of genes for most gut microbes. Analyses of a group of samples from Chinese and Danish individuals using IGC revealed country-specific gut microbial signatures. This expanded catalog should facilitate quantitative characterization of metagenomic, metatranscriptomic, and metaproteomic data from the gut microbiome to understand its variation across populations in human health and disease (Qin et al., 2010; Ferreira et al., 2014; Li et al., 2014). Recent studies show that changes in the commensal bacterial composition are linked to various metabolic and inflammatory diseases including inflammatory bowel disease (IBD; Sokol et al., 2008), obesity and type 2 diabetes (Everard et al., 2013; Dao et al., 2015), allergy (Berni Canani et al., 2015), and colorectal cancer (Swidsinski et al., 1998). These interrelationships provoke multiple fundamental questions regarding the cellular and molecular pathways through which commensal microbiota regulates mammalian gene expression and influence a wide range of clinically important diseased complications. The intestinal microbiota affects host physiology in many ways such as influencing the maturation of the immune response and fortifying the intestinal barrier against pathogenic bacteria. Importantly, intestinal microbes are potential regulators of digestion converting a wide range of non-digestible carbohydrates to short chain fatty acids (SCFA), which can be absorbed by the host and used as energy sources (Sharma et al., 2010; Becker et al., 2011).

Dysregulation of intestinal immune response by commensal microbiota plays an important role in the onset and development of different immune-mediated disorders (Wohlgemuth et al., 2009; Feng et al., 2010). For example, the presence of *Akkermansia muciniphila*, commensal mucin degrader, has been shown to exacerbate *Salmonella* Typhimurium infection by worsening intestinal inflammation, increasing macrophage infiltration and elevating proinflammatory cytokines

in gnotobiotic mice (Ganesh et al., 2013). Flagellin-detecting toll like receptor 5 (TLR5) knockout mice colonized with adherent-invasive *Escherichia coli* (AIEC) during microbiota acquisition drove chronic colitis. AIEC instigates chronic inflammation by increasing microbiota levels of LPS and flagellin (Chassaing et al., 2014). Recent findings described how commensals are recognized by the intestinal innate immune system and how individual species can influence specific modules of the innate and adaptive immunity. Germ-free mice were shown to have fewer and smaller Peyer patches, exhibit a local defect or absence of TH1, TH17, and TREG cells, and their intestinal epithelia express lower amounts of TLRs and MHC class II, as compared with mice that have been exposed to normal microbiota (commensals). Similarly, symbiosis factor polysaccharide A (produced by *Bacteroides fragilis*) can induce TREG cells and suppress TH17 cells via engagement of TLR2 on $CD4^+$ T cells (Round et al., 2011). Similarly, another human commensal *Faecalibacterium prausnitzii* suppresses IL-8 production and NF-κB signaling in response to inflammatory secretion of IL-1β (Sokol et al., 2008). Altogether, recent evidence has provided insights into immune-mediated mechanisms in metabolic disorders (Borchers et al., 2009). Taken all the findings together, existing data argues for the need to probe the microbiome for new strategies for immunomodulation, either by enhancing (immunodeficiency) or by suppressing (allergy) host immunity. Microbial metabolites and nutrients derived from beneficial bacteria in the intestine via luminal conversion may modulate host immunity and profoundly affect mammalian biology of the "holobiont."

CHANGES IN MICROBIAL DIVERSITY AND TREATMENT WITH PROBIOTICS

Recent studies in rodents show that inflammation and/or infection is correlated with changes in bacterial composition (Packey and Sartor, 2009; Saulnier et al., 2011; Pflughoeft and Versalovic, 2012; Ganesh et al., 2013). Molecular techniques are clarifying changes in the composition of the mucosal associated and fecal microbiota in patients with IBD esp., ulcerative colitis (UC), and Crohn's diseases (CD) together with widely expanding previous culture based studies. Patients with UC and CD have decreased complexity of commensal microbiota revealed by examining DNA libraries (Frank et al., 2007). More specifically, members of the phyla Bacteroidetes and Firmicutes are decreased in CD and UC patients (Backhed et al., 2005). A member of the family Firmicutes, *F. prausnitzii* was reduced in the patients with CD and this was confirmed and associated with increased risk of post-resection recurrence of ileal CD (Frank et al., 2007; Sokol et al., 2008; Swidsinski et al., 2008). *In vitro* peripheral blood mononuclear cell stimulation by *F. prausnitzii* decreased pro-inflammatory cytokines IL-12 and IFN-γ and stimulated secretion of anti-inflammatory cytokine IL-10. Oral administration of live *F. prausnitzii* or its supernatant reduced the inflammation severity by TNBS and corrected the associated dysbiosis (Baumgart et al., 2007). However, the abundance of *E. coli* is increased in IBD patients (**Figure 1;** Kotlowski et al., 2007). Similarly, the mucosal *E. coli* numbers *in situ* correlates with the severity of ileal disease and invasive *E. coli* are restricted to inflamed mucosa. Finally, fecal and mucosal associated microbial communities of UC and CD patients are consistently less diverse with increased instability. Commensal non-pathogenic bacteria can cause colitis in host with immunomodulatory and mucosal barrier deficits. Interleukin (IL)-$10^{-/-}$ germ-free mice colonized with *Enterococcus faecalis* and/or invasive *E. coli*, showed aggressive TH1/TH17-mediated colitis within 3 weeks but this was not observed in the WT mice. LPS from microbes were detected by dendritic cells (DCs). DCs play an important role through antigen presentation via TLRs in linking between the innate and adaptive immunity (McKenna et al., 2005). DCs are the initial cells to synthesize IL-12 under well characterized microbial stimulants of the cytokines. IL-12 selectively promotes the differentiation of Th1 $CD4^+$ cells upon stimulation with antigens (de Jong et al., 2002). Th1 cell-mediated immune response leads to the paradigm of T-helper cell differentiation in which IL-12 cytokine mediated activation of STAT4 and is critical for generation of Th1 cells (Kaplan et al., 1998). IL-12 mediated immune response is dependent upon the presence of $CD4^+$ and $CD8^+$ T lymphocytes and upon the production of IFN-γ finally causing cell-mediated adaptive immunity (**Figure 1;** Kim et al., 2007). However, certain class of bacteria like probiotic bacterium, *Bifidobacterium breve* increased IL-10 secretion Tr-1 cells in the colon and inhibits inflammation (Jeon et al., 2012). Introducing such beneficial strains in an unhealthy intestinal environment will potentially be a novel therapeutic strategy.

Most importantly, metabolites produced by intestinal microbiota have direct effects on the host mucosa. Commensal bacterial fermentation of non-digestible fiber leads to increased luminal bioavailability of SCFAs like butyrate, acetate, fumarate, and propionate (Cummings and Macfarlane, 1997). Bacterial metabolites such as butyrate serve as potential energy sources for colonic epithelial cells, whereas other fermentation by-products like hydrogen sulfide (HS), nitric oxide (NO) and proteases produced by subsets of commensals may enhance histopathology. Butyrate metabolism by colonic epithelial cells might be suppressed by HS/NO metabolites, resulting in starvation of colonocytes and yielding histopathology similar to that of UC (Roediger et al., 1993; Packey and Sartor, 2009; Cain and Karpa, 2011). The butyrate producing probiotic bacterium *Clostridium butyricum* MIYAIRI 588, increase the butyrate availability in the presence of fibrous diet (Weng et al., 2015). Intracellular butyrate and propionate (but not acetate) has been shown to inhibit the activity of histone deacetylases (HDACs) in colonocytes and immune cells, which promotes the hyperacetylation of histones, in addition to some transcription factors and proteins that are involved in signal transduction. This has multiple consequences for gene expression and cellular differentiation, including the down-regulation of pro-inflammatory cytokines, such as IL-6 and IL-12, in colonic macrophages and is also known to inhibit colorectal cancer (Louis et al., 2014). Similarly, pretreatment of *Helicobacter pylori*-induced gastric ulcers with *C. butyricum* in mice showed significantly reduced numbers of mucosal lesions with decreased quantities of proinflammatory cytokines (Wang et al., 2015). Probiotics may provide beneficial functions into the GI tract which might enhance the functionality of the

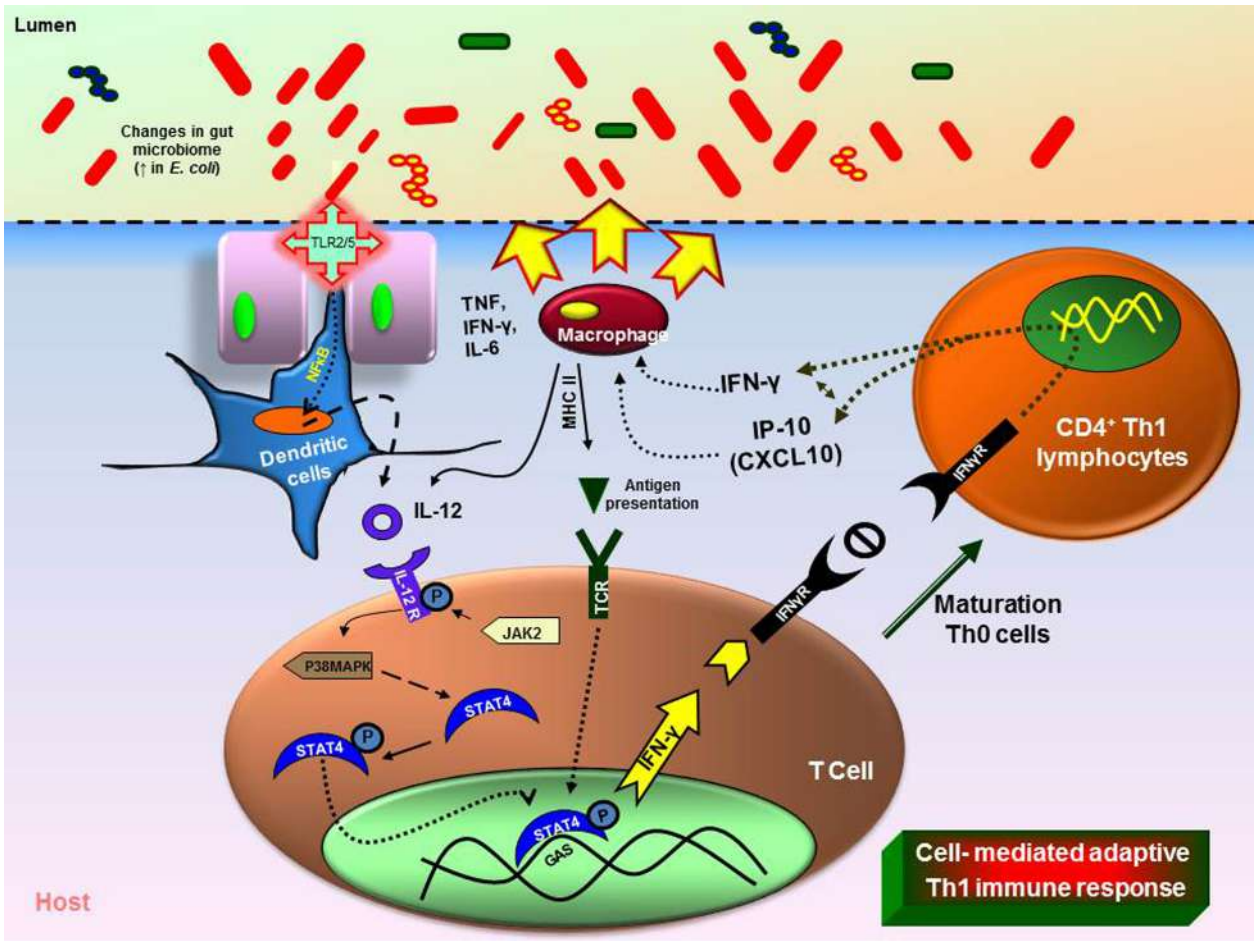

FIGURE 1 | Immune responses triggered by changes in the gut microbiome. Intestinal inflammation in the UC or CD leads to dysbiosis (imbalance microbiota). Overgrowth of enteropathogenic bacteria causing increased activation of toll-like receptors (TLR) 2 or 4. This causes the activation and translocation of nuclear factor kappa B (NFκB) and causes secretion of pro-inflammatory cytokine interleukin (IL)-12. Increased IL-12 causes T-helper (Th) Th1/Th2 immune response with increase in tumor necrosis factor (TNF), IL-6, interferon gamma (IFN-γ). The dysbiosis leads to increase in immune cells (macrophages, neutrophils) at the infected site causing severe inflammation (MHCII—major histocompatibility complex).

existing commensal communities. Probiotics may also affect the composition of the intestinal microbiota by providing colonization resistance and competition for nutrients or production of pathogenic inhibitors and modulates intestinal immune response.

Probiotics possess the ability to transiently colonize the gut (Valeur et al., 2004; Ukibe et al., 2015; Vieira et al., 2015) and facilitating proliferation of commensal microbes, while enhancing microbial diversity (Sherman et al., 2009). Probiotics are known to exert antimicrobial effects as a front line of defense against the luminal pathogens. For example, some probiotics are known to elaborate some microbial products known as bacteriocins. These probiotic factors can inhibit the growth and virulence of enteric bacterial pathogens (Corr et al., 2007). *Bifidobacterium animalis* subsp. *lactis* (*B. lactis*), *Streptococcus thermophilus*, two different strains of *Lactobacillus delbrueckii* subsp and *L. lactis* subsp in fermented milk were used to determine the impact of microbes in a mouse model of IBD. The findings show that *B. lactis* containing fermented milk decreased cecal pH, altered SCFA concentrations, increased the relative quantities of lactate- and butyrate-consuming bacteria, and reduced intestinal inflammation scores (Veiga et al., 2010). In addition, lactic-acid producing bacteria are known to exert antimicrobial effects on pathogens by reducing the pH of the microenvironment in the lumen of the GI tract (Fayol-Messaoudi et al., 2005). Probiotics or their metabolites reduced the secretion of immunomodulation molecule autoinducer-2 by the pathogenic *E. coli*, which results in reduced gene expression contained in the locus of enterocyte effacement (Pathogenicity Island) which is critical for mediating intimate bacterial binding to the host cell surfaces, called attachment and effacing lesion (Mack et al., 1999; Russell et al., 2007). *Lactobacillus plantarum* has been shown to have the capacity to enhance the production and secretion of mucins esp. MUC2 and MUC3 from the human intestinal epithelial cells (Mack et al., 1999), which improves the epithelial barrier function (Corfield et al., 1992, 2000). Similarly, bacteria and their by-products may have direct effect on the betterment of host health.

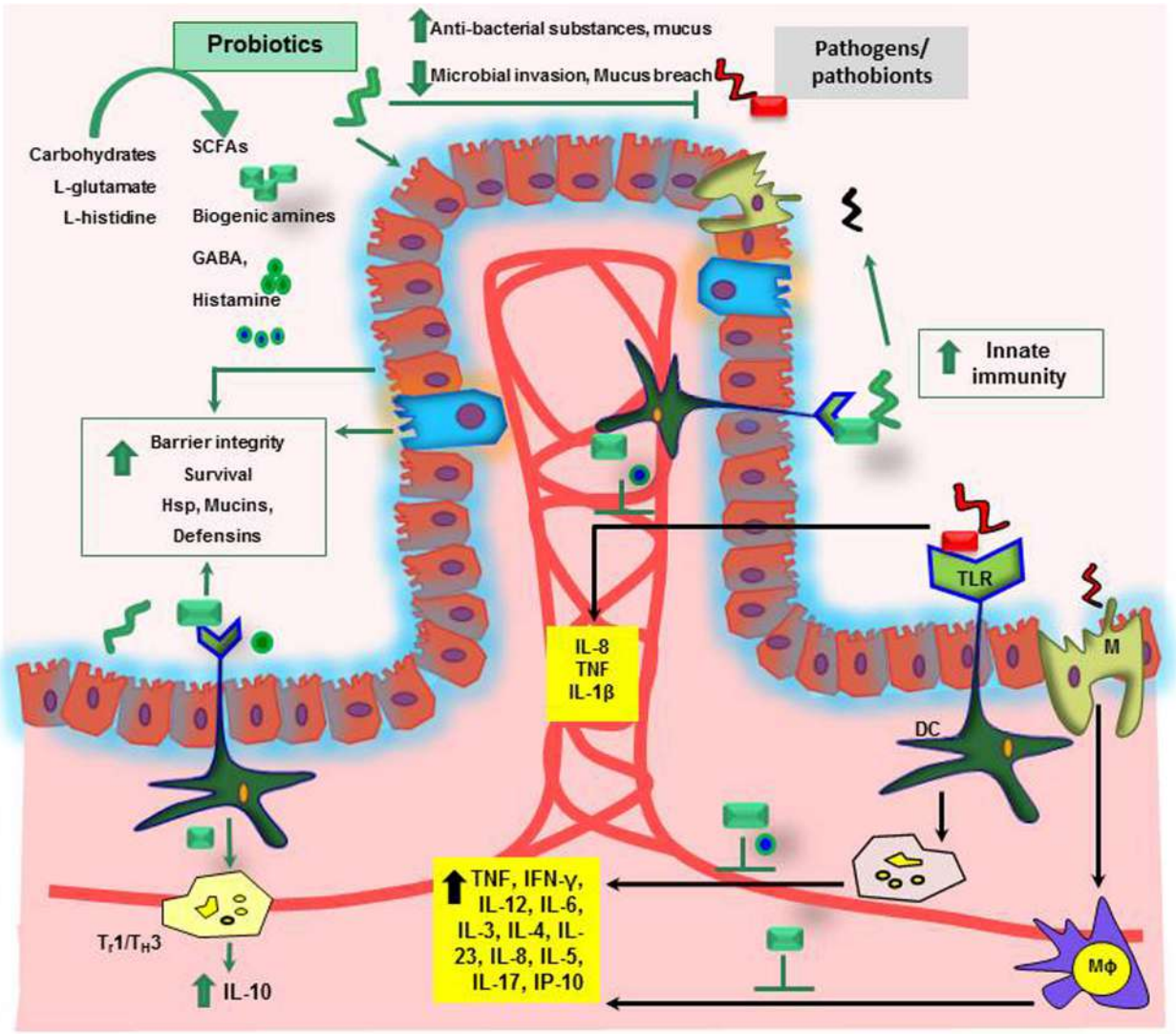

FIGURE 2 | Mechanisms of probiosis in the gastrointestinal tract. SCFAs, short chain fatty acids; GABA, gamma-aminobutyric acid; Hsp, heat shock proteins; IL, interleukin; TNF, tumor necrosis factor; Th, T-helper; IFN-γ, interferon gamma; Mϕ, Macrophage; DC, dendritic cell; M, microfold cells.

LUMINAL CONVERSION OF DIETARY COMPONENTS BY THE INTESTINAL MICROBIOTA

Human diet may have a direct impact on the intestinal microbiota which ultimately leads to the changes in the microbiota composition. These changes have been recently validated using mouse model experiments. Mice subjected to the high fat diet in obese mice showed major changes in microbial composition with an increased proportion of the phylum Firmicutes and decreased proportion of Bacteroidetes. In particular, species like *Clostridium ramosum* was correlated with increased body weight (Fleissner et al., 2010; Woting et al., 2014). Vitamins, amino acids or dietary fibers with the diet are assimilated and converted into other metabolites in the lumen by intestinal microbiota. Some of the products of these bio-chemical conversions were SCFA, biogenic amines (such as histamine) or other amino acid derived metabolites like serotonin or gamma-aminobutyric acid (GABA; Bravo et al., 2011; **Figure 2**) which may have beneficial effect on host health (Hemarajata and Versalovic, 2013; Hemarajata et al., 2013). Serotonin is a neurotransmitter, biochemically derived from tryptophan (Best et al., 2010). *Bifidobacterium infantis* colonization in rats modulated the bioavailability of tryptophan by yielding increased concentrations of tryptophan in plasma, reduced 5-HIAA (hydroxyindoleacetic acid) concentrations in the frontal cortex, and diminished quantities of 3,4-dihydroxyphenylacetic acid (DOPAC) in the amygdaloid cortex (Desbonnet et al., 2008). Gut microbial populations in SPF mice modulated brain development by contributing to suppressed expression of postsynaptic density protein (PSD)-95 and synaptophysin in the striatum compared to germ-free mice (Diaz Heijtz et al., 2011). Treatment with

Bifidobacterium species resulted in normalization of the immune response, reversal of behavioral deficits, and restoration of basal noradrenaline concentrations in the brainstem, thereby alleviating depression of the CNS (Desbonnet et al., 2010). In addition, orally gavaged BALB/c mice with *Lactobacillus rhamnosus* (JB-1) reduced $GABA_{A\alpha 2}$ gene expression in the prefrontal cortex and amygdala, but increased $GABA_{A\alpha 2}$ gene expression in the hippocampus. These findings provide evidence that *Lactobacillus* strains regulate emotions, behavior and central GABA receptor expression (Bravo et al., 2011). Intestinal microbiota may modulate the bioavailability of tryptophan in the intestine, and may in turn influence availability of neurotransmitters such as serotonin in the host. Non-digestible carbohydrates can be fermented in the lumen resulting in production of SCFAs such as lactate, formate, acetate, propionate, butyrate and valerate (Blaut, 2013). These metabolically active SCFAs are involved in various biological processes as an energy source in intestinal epithelial cell proliferation (Astbury and Corfe, 2012; Fung et al., 2012; Matthews et al., 2012). Additionally, fermentation of prebiotic carbohydrates such as inulin and fructo-oligosaccharides has been shown to increase the proportion of beneficial microbes like *Bifidobacterium* spp. and *Lactobacillus* spp. in the obese mice and was negatively correlated with serum entoxin levels (Salazar et al., 2014). Consumption of western diet showed increased level of plasma LPS concentration and this was correlated with increased changes in microbiota composition (Cani et al., 2013; Everard and Cani, 2013; Everard et al., 2013). Moreover, a recent study shows that dietary plant lignans were converted to estradiol like metabolite enterodiol and enterolactone by intestinal bacteria in germ-free rats colonized with lignan-converting consortium, such as *Clostridium saccharogumia*, *Blautia producta*, *Eggerthella lenta*, and *Lactonifactor longoviformis*. The produced enterolignans suppressed tumor number and tumor cell proliferation in hormone related cancer (Mabrok et al., 2012).

The secondary plant metabolites, glucosinolates from Brassica vegetables, were converted to isothiocyanates (glucosinolate derivative) and were measured in urine, luminal contents and plasma of mice (Budnowski et al., 2013). In addition, glucosinolates and their derivatives have been shown to reduce AOM/DSS induced colon carcinogenesis in mice (Lippmann et al., 2014). For example, *Bacteroides thetaiotaomicron* isolated from human fecal sample can convert glucosinolates into isothiocyanates, measured in luminal contents of rats (Elfoul et al., 2001; Krul et al., 2002), and these compounds potentially suppress lung cancer cell metastasis by inhibiting cell survival signaling molecules Akt and NFκB activation in human lung large cell carcinoma (Wu et al., 2010b). Similarly, isoflavones have been implicated in the prevention of hormone-dependent and age related diseases, including cancer (Birt et al., 2001; Scalbert et al., 2005; Geller and Studee, 2006; Usui, 2006). Intestinal bacteria, e.g., *Slackia isoflavoniconvertens*, play an important role in the metabolism of isoflavones, daidzein and genistein to equol (Chang and Nair, 1995; Rafii et al., 2003; Matthies et al., 2008, 2012). Based on the structural similarities of these bacterial by-products with estrogens, they bind to estrogen receptors and thus may prevent cancer progression (Matthies et al., 2008; Lepri et al., 2014).

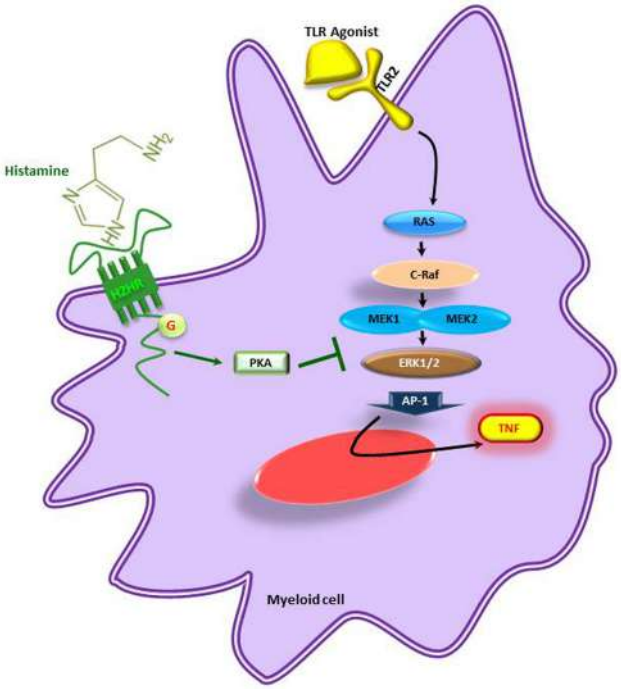

FIGURE 3 | Microbe-derived histamine mediated suppression of pro-inflammatory cytokines. TNF is suppressed by inhibition of the MEK/ERK pathway in myeloid cells. H2HR, histamine receptor 2; PKA, activated protein kinase A; TNF, tumor necrosis factor; TLR, toll-like receptor. Adapted from Thomas et al. (2012).

IMMUNOMODULATION BY PROBIOTICS

Probiotics (beneficial microbes) are frequently, though not necessarily be a commensal bacteria. Probiotics are defined as "beneficial live micro-organisms which when administrated in adequate amounts confer beneficial effects on the host health" (Mack et al., 1999; Peran et al., 2006; Borchers et al., 2009; Ganesh et al., 2012; Isolauri et al., 2012; Klaenhammer et al., 2012; Thomas et al., 2012; Morelli and Capurso, 2012; Arena et al., 2014; Dylag et al., 2014; Galdeano et al., 2015; Ki et al., 2014; Repa et al., 2014; Sah et al., 2014; Sanders et al., 2014). Most known probiotics until now are either lactobacilli or bifidobacteria representatives of which are normal inhabitants of the gastro-intestinal (GI) tract (Blum et al., 2002; Wohlgemuth et al., 2009). Recently, animal experiments and human studies suggest that therapeutic manipulation of the balance between beneficial and detrimental intestinal bacterial species can influence health and disease (Fitzpatrick, 2013). The known mechanisms of probiosis include manipulation of intestinal microbial communities, suppression of pathogens, immunomodulation, activation of anti-apoptotic genes in human or mouse intestinal epithelial cells from cytokine induced apoptosis, differentiation and fortification of the intestinal barrier (Thomas and Versalovic, 2010). For example, simultaneous treatment with probiotic *Streptococcus thermophilus* ATCC19258 and *Lactobacillus acidophilus* ATCC 4356, prevent invasion of entero-invasive *E. coli* and enhance the intestinal epithelial barrier function by amplifying the phosphorylation

of occludin and ZO-1 together with a reduction of pro-inflammatory responses *in vitro* (Resta-Lenert and Barrett, 2003). Another similar study also demonstrated that application of probiotic *E. coli* NISSLE (EcN) is able to mediate up-regulation of ZO-1 expression in murine IECs and confer protection from the Dextran sodium sulphate (DSS) colitis-associated increase in mucosal permeability to mice luminal substances (Ukena et al., 2007).

Loss of tolerance to the patient's own commensal microbiota has been implicated in the development of IBD (Wu et al., 2010a). Use of probiotics, to shift the existing microbiota balance in favor of protective microbial species and to treat IBD, has been extensively reviewed (Ochoa-Reparaz et al., 2009). The ability of some probiotics to synthesize bacteriocins (Awaisheh et al., 2013) or to induce the secretion of antibacterial cryptidins by Paneth cells (Hooper et al., 2003; Ayabe et al., 2004) could account for such changes in microbiota composition or even for the protection against pathogenic bacteria. In addition to the effects mediated by bacteria–bacteria interactions, probiotics may have a direct effect on host physiology. In the inflamed gut, the down-regulation of pro-inflammatory cytokines by probiotics may be an important factor for the observed improvement of symptoms (**Figure 2;** Ma et al., 2004). For example, *Lactobacillus casei* DN-114001 treatment increases the number of $CD4^+FoxP3^+$ regulatory T cells in mesenteric lymph nodes (mLN), decreases the production of the pro-inflammatory cytokines TNF-α and IFN-γ, changes the gut microbiota composition and prevents DSS induced colitis in BALB/c mice (Zakostelska et al., 2011). However, only few molecular mechanisms underlying probiotic action have so far been identified. Activation of TLR9 by bacterial DNA has been proposed as one possible mechanism of a probiotic-mediated amelioration of experimental colitis (Rachmilewitz et al., 2004). TLRs belong to highly conserved receptors of the innate immune system. TLR activation results in the translocation of the nuclear factor NFκB into the cell nucleus triggering transcription of immunorelevant genes (Cario and Podolsky, 2005). In addition, *L. casei* inhibits post-transcription of pro-inflammatory interferon γ-induced protein 10 (IP-10) in intestinal epithelial cells of colitic IL-10 knock-out mice (Hormannsperger et al., 2009).

An intact intestinal epithelial cell layer is of utmost importance for preventing the uncontrolled intrusion of pathogenic bacteria. However, pathogenic bacteria are capable of compromising the integrity of the epithelium by disrupting the tight junctions between epithelial cells (Berkes et al., 2003). Bacterial factors improving epithelial integrity have been identified for the probiotic *Lactobacillus* GG. This strain produces two soluble proteins (p40 and p75) which protect epithelial cells from apoptosis and thereby increase mucosal integrity. The secreted proteins activate anti-apoptotic protein kinase B (PKB/Akt) in a phosphatidylinositol-3′-kinase (PI3K)-dependent pathway and inhibit the pro-apoptotic p38/mitogen-activated protein kinase (MAPK; Yan et al., 2007).

Similarly, the biogenic amine, histamine, produced by decarboxylation of amino acid L-histidine by histidine decaxboxylase gene cluster (*hdc*) in *Lactobacillus reuteri* ATCC 6475 showed immunomodulatory effects by suppressing TNF production in myeloid progenitor cell lines (**Figure 3**) whereas the *L. reuteri* lacking *hdc* gene cluster was unable to suppress the pro-inflammatory cytokine TNF. The bacterial derived histamine binds to and activates histamine receptor H2 (HRH2) and there by inhibits MEK/ERK MAPK signaling pathway and presumably suppress TNF transcription and Ap-1 translocation (Thomas et al., 2012). These findings clearly demonstrate that bacterial interactions directly or indirectly have an impact on host physiology. Therefore, in the current review we mainly focused on the different beneficial bacteria and their metabolites on immunoregulation of the host.

CONCLUSION

In the presented review we demonstrated how probiotic bacteria or their metabolites regulate immunomodulatory effects on the host health. Probiotics have been proposed as preventive and therapeutic measures in order to restore the healthy microbiota composition and function of the GI tract. Additionally restoring the current balance is very important because the commensal bacteria are important source of vitamins, amino acids and lipid homeostasis and alternation in the levels of these metabolites might have an influence on the immune system (Brestoff and Artis, 2013). Therefore, therapeutic manipulations of intestinal bacteria by selectively altering the beneficial versus detrimental species by probiotics and or prebiotics administration could reverse the inflammatory responses and restore mucosal homeostasis. Future challenges include interrogations of molecular mechanisms through nutrients and beneficial bacterial metabolites, regulate immune response and linking the commensal bacteria-beneficial probiotic bacteria-metabolite-immune system axis in the content of health and diseases, may provide useful insights for the development of improved, preventive and therapeutically cost-effective and non-toxic approaches to treating different disorders mainly IBD.

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A nutrition strategy to reduce the burden of diet related disease: access to dietician services must complement population health approaches

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Poor diet quality is implicated in almost every disease and health issue. And yet, in most advanced market economies diet quality is poor, with a minority meeting guidelines for healthy eating. Poor diet is thus responsible for substantial disease burden. Societies have at their disposal a range of strategies to influence diet behaviors. These can be classified into: (i) population level socio-educational approaches to enhance diet knowledge; (ii) pricing incentives (subsidies on healthy foods, punitive taxes on unhealthy foods); (iii) regulations to modify the food environment, and (iv) the provision of clinical dietetic services. There is little evidence that societies are active in implementing the available strategies. Advertising of "junk foods" is largely unchecked, contrasting with strict controls on advertising tobacco products, which also attract punitive taxes. Access to dieticians is restricted in most countries, even in the context of universal health care. In Australia in 2011 there were just 2,969 practicing dieticians/nutritionists or 1.3 clinicians per 10,000 persons, compared with 5.8 physiotherapists per 10,000 persons, 14.8 general practitioners (family physicians) per 10,000 persons or 75 nurses per 10,000 persons. It is time to implement comprehensive national nutrition strategies capable of effecting change. Such strategies need to be multi-component, incorporating both public health approaches and expanded publicly funded dietetic services. Access to individualized dietetic services is needed by those at risk, or with current chronic conditions, given the complexity of the diet message, the need for professional support for behavior change and to reflect individual circumstances. The adoption of a comprehensive nutrition strategy offers the promise of substantial improvement in diet quality, better health and wellbeing and lower health care costs.

Keywords: nutrition strategy, dietician services, diet quality, population health

Diet Quality and Health

It is uncontentious that diet quality has a major impact on health. This is not simply relational, which it certainly is—populations with better diet quality are shown consistently to have better health outcomes (Keys et al., 1986; Sofi et al., 2008; Lai et al., 2014), but it is undeniably causal. Causality has been demonstrated from rigorous studies investigating causal pathways whereby specific nutrients

affect health (Parletta et al., 2013) and through the success of high quality intervention trials such as those incorporating the Mediterranean diet (de Lorgeril et al., 1999; Estruch et al., 2013).

The beneficial effects of a healthy dietary pattern derive from the cumulative and synergistic effect of nutrients from varying food sources. A healthy dietary pattern is widely agreed to be one that is high in fruit and vegetables, whole-grains and fish. Whereas, an unhealthy dietary pattern is high in fried foods and processed meats, refined grains and "extras" such as sugar laden drinks and confectionary (NHMRC, 2014). The key nutrients or foods responsible for the observed health benefits include (but are not limited to) antioxidants, omega-3 polyunsaturated fatty acids (PUFAs) and B vitamins (Parletta et al., 2013). The antioxidants in fruit and vegetables have a protective effect for health and the high content of omega-3 PUFAs from fish have vascular and anti-inflammatory properties (Akbaraly et al., 2009). Some of the health benefits of a recommended diet are now understood to operate through the gut microbiome, which is emerging as an important issue in human health and the development of chronic diseases (Kouris-Blazos and Itsiopoulos, 2014). Unhealthy diet patterns can be associated with pro-inflammatory changes, endothelial dysfunction and insulin resistance (Sánchez-Villegas et al., 2013). A poor quality diet involving excess saturated fat, *trans*-fatty acids, and omega-6 PUFAs has a high glycaemic load and provides insufficient fiber and essential micronutrients (Simopoulos, 2011). A full understanding of how key nutrients affect health is complex, and beyond the scope of this paper.

The effect of diet on health is observed at all stages of disease. It is implicated in the development of disease, as demonstrated in trials of dietary interventions to reduce the incidence of type 2 diabetes in persons with impaired glucose tolerance (Eriksson and Lindgärde, 1991), or in the incidence and prevalence of depression (Opie et al., 2013; Sánchez-Villegas et al., 2013). Diet quality is implicated in the rate of complications, including in those with advanced disease. The seminal Lyon Heart study of persons following a first heart attack (AMI), found that the risk of a major cardiac event was reduced by 66% for those randomized to a Mediterranean diet (de Lorgeril et al., 1999). Diet quality has been demonstrated to affect the rate and quality of recovery after major surgery (Cerantola et al., 2011) and is a critical factor in successful aging (Hodge et al., 2014).

The evidence is clear that diet quality, including diet composition (e.g., macro and micronutrient profile) is critical to health. Diet plays a role in disease incidence, development of complications, disease management, recovery, and quality of life. Diet quality is pertinent across virtually all health conditions; including cancers (Sofi et al., 2008), cardiovascular disease (Estruch et al., 2013), diabetes (Esposito et al., 2010), neurological (including Parkinsons and Alzheimers; Sofi et al., 2008), mental health (Sánchez-Villegas et al., 2011), maternal and child health (Thorton et al., 2009), and gastrointestinal disorders (Heizer et al., 2009).

Obesity (i.e., BMI $\geq$ 30 kg/m^2) has an impact on health. But it is body fat and specifically intra-abdominal fat mass that is the primary determinant of obesity-related morbidity (Dalton et al., 2003). Considering the complexities of the role of diet quality, the preoccupation with caloric restriction and weight loss is not justified by the evidence. It is not uncommon for dietary intervention trials to improve diet quality with improvements in health outcomes, independent of weight change (Itsiopoulos et al., 2011). The predominant focus on obesity as the *primary* dietary related issue could conceivably hinder adoption of the best policy response diverting the focus from diet quality.

There is an accumulating evidence base as to what constitutes a healthy diet. Specifically the health benefits of the Mediterranean diet are now widely confirmed by systematic reviews of intervention studies and cohort studies (Serra-Majem et al., 2006; Sofi et al., 2010). This diet is high in vegetables, legumes, fruits and nuts, fish, unrefined cereals, olive oil, low-to-moderate intake of dairy products and low in meat and "extras."

Average diet quality is poor in most advanced market economies with their abundant access to highly processed foods, that are strongly marketed. A recent food and nutrition survey in Australia found that only 5.5% of Australian adults have an adequate usual daily intake of fruit and vegetables (Australian Bureau of Statistics, 2014). Over one-third (35.4%) of total energy consumed was from "discretionary foods" of little nutritional value and high in sugars, saturated fats, salt and/or alcohol (Australian Bureau of Statistics, 2013). Diet related diseases continue to rise as reported in the Global Burden of Disease (Lim et al., 2012).

Aims

Given the poor quality of the average diet, it is clear that current approaches to improving public nutrition are failing. Effective strategies are urgently needed. The remainder of this paper is concerned to understand the reasons for this failure and define the components of an efficient nutrition strategy. As with any behavior change strategy this will need to contain multiple reinforcing elements.

Policy Elements to Improve Diet Quality

Public/Population Health Approaches

Population level education and information

The abundance of dietary information freely available from TV advertising, magazine and newspaper articles, blogs, celebrity books and the like, creates confusion among the public about what constitutes a healthy diet. In these forums having a dietary qualification is not a prerequisite for providing dietary advice. The fact that the population, including some health professionals, is unclear about what constitutes a healthy diet is not surprising. The subject is complex and even the scientific literature can be contradictory. Perhaps glaring in this regard has been confusion by the population and health professionals over the "low fat" message, which has had perverse consequences with fats being replaced by sugars (for example in yogurts), often a worse alternative. The complexity is in stark contrast to another behavioral risk factor, that of tobacco smoking, for which the message could not be simpler: "do not smoke." At the same time the population is exposed to a range of mediums advertising unhealthy foods: TV, print, radio, billboards and point of sale. Such exposure cannot be avoided and is often targeted at

children, increasing consumption of low nutrient calorie dense foods. If it did not work, companies would not be spending the billions of dollars on such advertising. Perversely, societies are actually *subsidizing* companies to encourage people to purchase unhealthy snacks and other high sugar foods (including some breakfast cereals, sugary drinks, etc.) through tax deductibility of advertising expenditure (as a business cost).

A number of activities can be employed to improve public information about diet. These include:

- *Social marketing campaigns*, which must be well-designed and draw on evidenced-based information. A core task is to describe the components of a healthy diet—what to eat more of; and what are unhealthy foods to eat less of. In Australia, public nutrition campaigns have been very poorly funded, in effect limiting any possible chance of success and have focused almost exclusively on promoting fruit and vegetable consumption, largely ignoring the issue of unhealthy foods. While successful marketing campaigns (for example to reduce road traffic accidents), have been very well resourced (millions of dollars compared with a few hundred thousand). These campaigns have also been supported by powerful legislative elements—in the case of road traffic accidents including mandatory seat belt legislation, large speeding fines with potential loss of license, all well-enforced.
- *Product labeling* is the second element in public education concerning diet. Developing a system that is informative and correct but also simple has proved elusive, despite considerable research and debate on this issue The core challenge is to create a system of labeling and nutrition information panel that consumers can understand and interpret in the context of their whole dietary pattern. While the simplified systems may seem appealing they all suffer from the complex nature of diet quality.
- *Restrictions on advertising of unhealthy foods*, especially on television and in "children viewing times" has been widely discussed, but rarely adopted. This is despite good evidence that higher TV viewing time is associated with poor diet quality and obesity (National Preventative Health Taskforce, 2009). The policy is viewed as difficult to implement—in terms of defining unhealthy foods and drinks to be targeted and arguments that it will not be effective, given children view television outside of "children viewing times." There are strong vested interests keen for such a policy not to be adopted.
- *Actively promote dieticians as the best source of expert nutrition advice*. Most individuals no longer know where to find evidence-based nutrition information or which health professionals to trust. Ways of ensuring the integrity of dietary advice provided to the public need to be explored, for example, to confirm the level of evidence supporting specific claims or advice. The public need to be provided with better guidance on where to obtain high-level nutrition information and which health professionals can provide this. (When is your favorite magazine a reliable source of nutrition information?)

Pricing strategies to promote purchases of healthy food and discourage purchases of unhealthy foods

Consumers respond to absolute and relative prices; purchases increase when prices fall and reduce when prices increase. Consumers also respond to the prices of complementary or substitute goods—known as the cross-elasticity of demand. For example, if the tax on beer goes up, consumers may reduce consumption but will also switch to wine or spirits. Punitive taxes on unhealthy products could be used to discourage purchases, and subsidies on healthy products could be used to encourage consumption (Black et al., 2013). Food vouchers/stamps are a variant of the latter (Guthrie et al., 2007).

Punitive taxes have been used widely to discourage purchases of tobacco products (and are an efficient, albeit inequitable way of raising revenue). Internationally, most countries apply excise duty on tobacco products. Excise is typically specified as an amount payable per *x* cigarette sticks (Chaloupka et al., 2010). Across the OECD countries, tobacco taxes account for between *43 and 80%* of the purchase price of a packet of cigarettes. In 12 of 16 countries tobacco taxes account for *over 70%* of the purchase price (World Health Organization, 2013, Table 9.2.0 Appendix IX). This equates to a punitive tax of between *230 and 400%* on the base price, making cigarettes three to five times as expensive as they would be otherwise. This is a serious policy platform.

Conversations about penalty taxes to change eating behaviors, for example on high saturated fat or high sugar foods have by contrast been canvassing only *very* small tax penalties of around 10–20%. Placing punitive taxes on foods is more problematic than for tobacco products. The logistics are challenging. It is necessary to select the products or food components on which to place punitive taxes, the best method of taxation needs to be determined, e.g., per gram of sugar or fat, or per item falling within designated descriptors. The possible switching of purchases by consumers needs also to be considered. For example, if punitive taxes were placed on drinks with high added sugar, this would increase demand for substitutes such as artificially sweetened drinks, or fruit juices, not necessarily a desired response. The highly contentious tax on saturated fat introduced in Denmark in 2011 and rescinded just 12 months later illustrates the challenge. The fat tax was faced with both political and operational challenges (The Economist, 2012). While some evidence of favorable behavior change was reported (Smed, 2012; Jensen and Smed, 2013), undesirable consequences were also observed, for example with people shopping outside Denmark. A plan to introduce a sugar tax in Denmark was shelved. This is disappointing especially as a tax on sugar makes more sense, in terms of likely health impact than a tax on fat. If implemented it would have created a valuable natural experiment to inform diet policy across the OECD. But again the policy came up against powerful vested interests.

Subsidizing fruit and vegetables and other healthy foods, while common, can have only a small impact on purchases (Bihan et al., 2011; An, 2013). Studies suggest the elasticity of demand for fruit and vegetables is around 0.5 (Powell et al., 2013). Thus, a fall in price of x% would be associated with an increase in consumption of 0.5×. This means for example in Australia, where average consumption of vegetables is ∼2 serves per person per day

(Australian Bureau of Statistics, 2013), a 30% reduction in price is predicted to increase consumption by 15% (i.e., by 0.3 serves per day). Hence, mean vegetable consumption would increase to 2.3 serves per day, which is still considerably less than the recommended five serves per person per day. That is, the potential size of impact from even quite generous subsidies will be small, but the cost would be considerable in providing the subsidy and in the costs of implementation. Subsidies are logistically challenging to implement. This is not to say that the issue of access to high quality, affordable healthy foods is not important and especially in more isolated communities; but a subsidy on healthy foods is unlikely to be the most effective or efficient way to ensure better access.

Punitive taxes on unhealthy foods could, in contrast have a considerable effect. Demand is more elastic—a price increase on sugar sweetened beverages is predicted to result in at least an equal percent reduction in demand. Extras form a large part of unhealthy diets, so that the effect of a price increase could be substantial. Consider a punitive tax of 50% on soft-drinks, confectionary (including ice-cream), cakes, pastries etc. (that make up ∼80% of extras); this would be predicted to reduce demand for these products by ∼50%. In Australia, where extras constitute 30.6% of the diet, in terms of energy excluding alcohol (Australian Bureau of Statistics, 2013), a 50% fall in consumption would bring extras down to <16%, which is a substantial improvement in diet quality. The policy would also raise revenue. The key challenges are political, given the vested interest that would be affected, and logistical.

Changing the food environment

There are a number of possible strategies for changing the food environment as described below:

- *Regulations*—can be promulgated to modify the food environment. Options include (a) proscribing the constituents of food products (e.g., to restrict allowable levels of salt or sugars); (b) the use of zoning provisions, say to limit access to fast food outlets within a defined distance of a school, or to control the density of fast food outlets within vulnerable communities; (c) regulating sale of selected "unhealthy foods" by venue and/or customer (e.g., proscribing foods allowed to be sold or served in school canteens, hospitals, residential facilities or restricting sales of alcohol on premises and take-away by age of customer, hours of opening or customer alcohol history).
- *Working collaboratively with suppliers/industry*—is another option for achieving change in the food supply which may be more politically acceptable and is illustrated by campaigns to reduce the salt content of processed foods. A collaborative salt reduction program in the UK achieved a significant reduction in mean salt intake between 2000/01 and 2011 from 9.5 to 8.1 g per person per day (Department of Health UK, 2012). Agreements to include nutrient supplements in foods have also proceeded through a mix of mandatory and voluntary schemes. Debate continues around the best strategies to fortify breakfast cereals/breads with folic acid (Dalziel et al., 2010).
- *Community-level initiatives*. A wide variety of approaches have been used by communities in an attempt to change the food environment and at the same time actively engage communities in strategies to improve diet quality. Examples include various kitchen garden programs, which demonstrate some success (Hume et al., 2014), programs to make clean fresh cool water more available in schools or in remote communities, and community based obesity prevention programs, such as the French EPODE program (Borys et al., 2012). These programs have mixed success (Dalziel and Segal, 2007).

Clinical strategies

Population health strategies can never provide the complete approach to improving the diet. Even with tobacco smoking, which is perhaps the best possible case for population health approaches given the simplicity and clarity of the message, strong public support for legislative intervention and punitive pricing, a substantial clinical program was necessary to achieve the observed behavior changes. These have included funded quit-smoking phone lines, funded quit products (prescription drugs and nicotine patches/products) together with a clear and consistent message from health professionals.

Diet is complex. Simple public health messages can never convey a full understanding of how to construct a healthy diet. Knowledge dissemination in isolation will not achieve sustained dietary improvements. Adopting a better diet requires an understanding of how a current diet might be improved which requires detailed knowledge of the nutritional composition and role of individual foods and food groups, but also contextualized for the individual. Achieving sustained change requires an understanding of barriers and ambivalence to change, but also a knowledge of individual preferences, cultural/cooking traditions, cooking skills, access to foods, food preparation and storage facilities, lifestyle, and family circumstances. This complexity points to the need for individualized dietary advice by a trained and skilled practitioner. A recent review of dietary interventions found that the likelihood of achieving desired behavior change and improved diet quality is greater where qualified dieticians are used (Opie et al., 2013). Accredited Practicing Dieticians are equipped to provide current, evidence-informed nutrition advice and are trained in counseling skills that can address ambivalence and barriers to change, using empowering approaches.

While it is desirable to provide high quality information to the public about healthy diets and a better informed consumer will improve the signals to the food industry (Segal, 1998a,b, Watts and Segal, 2009); population health approaches are not an alternative to funded access to individualized dietary advice and support, but rather a complement.

Most health systems, even those with a strong commitment to universal coverage and public funding, limit subsidized access to dietetic services, whether in the community or hospital in-patient or out-patient settings. Unlike medical and nursing, it is difficult to find international comparisons of access to dietetic services. In Australia, based on the 5-yearly population census that records information on qualification and occupation, in 2011 there were just 2,969 practicing dieticians/nutritionists. This was equal to 1.3 per 10,000 persons, far less than the 5.8 physiotherapists per

10,000 persons or 14.8 General Practitioners (family physicians) per 10,000 persons or 75.0 nurses per 10,000 persons. Most (95%) dieticians/nutritionists are employed in the health/human services sector, many are part-time. Australia thus has approximately one full time equivalent FTE dietician/nutritionist per 10,000 persons. Given the high rates of nutrition related chronic disease and risk which including high blood pressure, high cholesterol, obesity which affect over 50% of adults, it is inconceivable that the current level of dietetic services is adequate.

Additional dietetic positions are needed to ensure access to dietetic services for those with, or at risk of, diet related health conditions. Highly subsidized dietetic services are needed in the community as part of multi-disciplinary primary care teams delivering chronic disease management and prevention and in the hospital in-patient and out-patient settings. If dietetic services are available only on a fee-for-service basis, many in need will fail to access these services, to the detriment of their health, with flow-on implications for the health system and the wider economy. Failure to access multi-disciplinary best practice care is widely reported and funding and delivery arrangements are implicated (Watts and Segal, 2009).

Dieticians need to be available in hospital in-patient and out-patient settings to support patients to adopt healthy eating behaviors. And yet, they are typically regarded as expendable in the face of the inevitable budget pressures. Best practice care would dictate that all cardiac rehabilitation patients, pregnant women (especially those who are obese), mental health patients, persons with diabetes and patients with other conditions for which diet is an established risk factor, have access to individualized professional dietetic services. This simply is not happening in either public or private hospital settings, despite evidence that many dietetic interventions are effective and cost-effective (Dalziel et al., 2006; Dalziel and Segal, 2007).

Dieticians are also needed to work in institutional settings that serve food, many of which involve highly vulnerable populations to improve food quality, for example aged care facilities, preschools, prisons, etc.

Access to high quality professional dietetic advice and support must be a core part of any comprehensive strategy to improve population diet. There is a widespread view that "dietary interventions do not work," and yet the accumulating evidence of highly successful RCTs suggests the opposite. Success is especially apparent where outcomes are expressed in terms of change in clinical/health outcomes (such as stroke, heart attack, death, incidence of diabetes), rather than intermediate risk markers. Studies with longer term follow-up targeting persons with current diet related disease/risk factors demonstrate particular success, for example in persons with impaired glucose tolerance that report significantly lower rates of progression to type 2 diabetes in intervention group patients (Eriksson and Lindgärde, 1991).

Major Risks to Implementation

Any attempt to introduce punitive taxes will create winners and losers. The losers will be highly vocal in resisting change, regardless of the potential public benefit. This is the nature of vested interest. Where there is any doubt about the ability to define and target unhealthy foods, political hurdles are magnified. This is illustrated in the Denmark fat tax example. A common response to regulatory approaches is the cry of "nanny state": that people should be free to make their own choices without interference from government. This response ignores the context in which people make choices. The unfettered behaviors of suppliers and consumers will only be efficient under conditions of the "perfect market." This requires fully informed consumers with complete knowledge about the products and services available to them and of their impact on their health and wellbeing; free entry and exit whereby no firm can exercise monopoly power (a condition violated by the pharmaceutical industry or in the delivery of clinical services); an absence of externalities—benefits do not extend beyond the consumer or costs beyond the suppliers. This is demonstrably violated in relation to diet, where the wider community bears in part the costs of poor diet quality in higher health care expenditures and lower workforce productivity, costs which suppliers of unhealthy foods fail to bear. There is every reason for governments to intervene. It is demanded by the pervasiveness of market failure (Segal, 2010).

Unfortunately those who stand to gain from an effective strategy to improve diet quality are inevitably less vocal, partly because losses and potential gains are not viewed equally and partly because the general population, which stands to gain, is more diffuse and less powerful. Furthermore the average citizen does not necessarily understand how current distortions are damaging their health. Those who stand to gain most, are persons suffering from, or at risk of, diet related disease, as well as farmers and retailers growing and selling predominantly whole foods. Dieticians would also benefit from expanded employment opportunities. However, none of these groups constitute powerful lobbies.

If punitive taxes were part of the strategy it could be revenue neutral. But if not; it will be said that "there are no funds." To implement a well-developed public information campaign or expand funding of dietetic services will represent an additional cost. But, diet-related illnesses are the major cost on health budgets and also on the economy in lost productivity, lost production and welfare dependency from premature mortality and disability (from mental and physical illness). In the latest Global Burden of Disease Study (Lim et al., 2012), three of the four top risk factors in advanced western countries are diet related—high blood pressure, obesity and high blood glucose. The potential payoff from improving the eating behaviors of the population is thus considerable. If policies target persons with current diet related conditions, or at high risk, returns on the investment will accrue almost immediately. For example, a dietary intervention to improve eating behaviors in obese pregnant women would deliver health benefits and budget savings within months, through expected lower rates of gestational diabetes and better mother and child outcomes (Thorton et al., 2009; Opie, 2014).

Conclusion—Core Components of a Nutrition Strategy

It is time to get serious about developing and implementing national nutrition strategies that are capable of effecting change.

Multi-component strategies are needed that incorporate social marketing, regulatory restrictions on advertising of junk food/drinks, punitive taxes on unhealthy foods, suitable food labeling and publicly funded dietician services. Dietetic services need to be viewed as part of core heath service delivery and funded at a level that supports access to individualized dietetic services by persons at risk and with current chronic conditions.

While there is considerable pessimism about the ability to improve diet quality across a population, the absence of any comprehensive approach to date, rather gives room for optimism. It is not that we have tried and failed. It is that we have *not* tried and failed. The evidence is clear—diet affects health and is modifiable. Accumulating evidence from intervention studies with long term follow-up demonstrate that eating behaviors can change. But that individualized clinical advice and support is required from highly skilled and trained professionals. If a comprehensive nutrition strategy were adopted, the promise is a substantial improvement in diet quality, better health and wellbeing and lower health care costs. All that is needed is political will and some upfront investment with likely early payoff.

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

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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 mellitus (GDM) and associated with increased morbidity for mother and child in the perinatal period. Poorly controlled diabetes during pregnancy, pre-pregnancy 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, 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 life style, 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.

Keywords: maternal overweight, gestational diabetes mellitus, macrosomia, health economics, public health burden

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 second birthday (Morton, 2006; Black et al., 2008). 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 (Johnson and Schoeni, 2011).

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 >4000 g regardless of gestational age (Boulet et al., 2003; Costa et al., 2012). The incidence of macrosomia ranges from 12.8 to 37.4% worldwide (Rodrigues et al., 2000; Kac and Velasquez-Melendez, 2005; de Oliveira et al., 2008). 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 mellitus (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 (Shi et al., 2014). In developing countries maternal short statue, high body mass index (BMI), and T2DM are strong risk factors for macrosomia (Koyanagi et al., 2013).

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 cesarean delivery (HAPO Study Cooperative Research Group et al., 2008; Henriksen, 2008; Jastrow et al., 2010). For the macrosomic infant, birth trauma is commonly related to instrumental delivery, e.g., newborns with a birth weight >4000 g have 9.0 times higher odds of shoulder dystocia, while those with a birth weight >4500 g have odds that are 39.5 times higher than normal-weight infants (Robinson et al., 2003). Furthermore, macrosomic infants are more likely to have low 5-min Apgar scores, an index of hypoxia (Johnson and Schoeni, 2011). Infants with very severe macrosomia (birth weight >5000 g) are at increased risk of neonatal, post-neonatal and infant death (Boulet et al., 2003). Macrosomia also significantly increases the risk for developing obesity in childhood, and non-communicable diseases (NCD) later in life (Morton, 2006).

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 (Parsons et al., 1992; Kawai and Kishi, 1999; Clapp, 2006). 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 pre-pregnancy obesity and/or excessive GWG, have a higher risk for developing GDM, pregnancy-induced hypertension, cesarean delivery, and LGA and macrosomic infants compared to women with normal pre-pregnancy BMI and adequate pregnancy weight gain (Li et al., 2013).

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 preeclampsia in comparison to their normal-weight counterparts (Bodnar et al., 2010). 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 (Black et al., 2013). Similarly, a 13-years study of 292 568 singleton pregnancies in China (Liu et al., 2012) demonstrated that adverse pregnancy outcomes, such as hypertensive disorders, cesarean delivery, macrosomia, and LGA infants, were associated with overweight mothers, who during pregnancy gained weight beyond current IOM recommendations (Institute of Medicine/National Research Council, 2009).

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 (Tanvig et al., 2013). 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 (Egan et al., 2014).

Altogether, these studies emphasize that high pre-pregnancy 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 cesarean section before weeks 40 of pregnancy (Poston et al., 2011).

Gestational Diabetes Mellitus

In women already prone to insulin resistance because of obesity or (epi) genetic predisposition (Vaag et al., 2014), this physiological tendency is augmented and can result in the development of GDM, commonly diagnosed around weeks 20–24 of pregnancy. A study including 35 253 pregnancies in Australia showed an average incidence of GDM of 5.5% ($n = 1928$; Beischer et al., 1991).

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 (Ferrara et al., 2004; Rosenberg et al., 2005; Hunsberger et al., 2010). 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 (Jiwani et al., 2012). 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 (Zawiejska et al., 2014). Adoption of the HAPO criteria for GDM diagnosis will likely lead to higher GDM prevalence compared to current estimates (Jiwani et al., 2012), although still considerable differences in incidence as well as relevance of the different hyperglycemia measures were reported between the participating HAPO centers (Sacks et al., 2012).

Objective

The primary objective of this study was 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 (Henriksen, 2008; Ma and Chan, 2013).

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 (Weinstein and Fineberg, 1980). 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 (Lenoir-Wijnkoop et al., 2011).

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 modeling of GDM and obesity 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

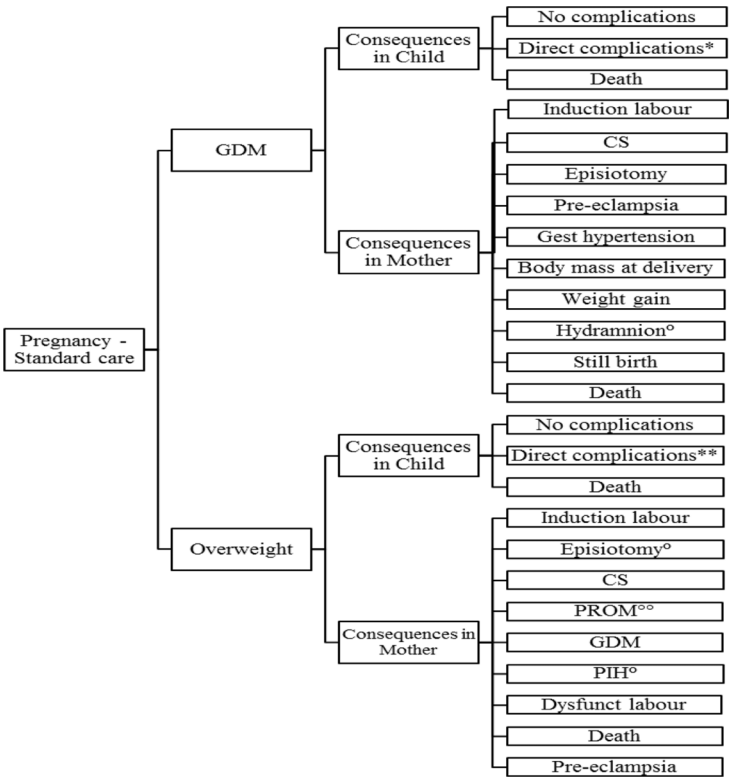

FIGURE 1 | Structure of the model. Reported events are based on literature: *Includes respectively, hypoglycemia, hyperbilirubinemia, prematurity, macrosomia, brachial plexus injury, shoulder dystocia, respiratory distress, NICU admission; **Includes respectively, prematurity, macrosomia, NICU, stillbirth, IUGR; °Only reported for GDM (Michlin); °°Not reported for GDM.

(preexisting) 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 keywords: 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 (Lampe et al., 2009).

Incidence

The incidence rate used for our model was 5.5%, derived from the study outcomes reported by Beischer et al. (1991). This is a conservative value, taken into account the incidence rates reported above (Ferrara et al., 2004; Rosenberg et al., 2005; Hunsberger et al., 2010), 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 (Henriksen, 2008).

Complications

Studies reporting the risk of perinatal adverse outcomes for mother and child in the case of obesity (Galtier-Dereure et al., 1995; Michlin et al., 2000; Pathi et al., 2006; Salihu et al., 2011), mild GDM (Landon et al., 2009; Ohno et al., 2011), and total GDM (Keshavarz et al., 2005; Reece, 2010; Mission et al., 2012)

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

Mild GDM								**Source**
Outcomes								**Landon**
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**
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**
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 significance	NS	S	S	S	S	NS		

**Statistical significance not reported.*

show that not all complications are statistically significant. Data input on obesity is derived from Salihu et al. (2011) because of the large sample size of obese women (**Table 1**), whereas for GDM the data for mild GDM are used (Galtier-Dereure et al., 1995; Pathi et al., 2006), taking a conservative approach. Mission et al. (2012) 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. (2005) on the probability of hydramnion and stillbirth (respectively, 0.60 and 0.40%).

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
Macrosomia	No treatment GDM vs. control	2.66	1.93–3.67	Langer
Macrosomia	Treatment vs. control	1.13	0.82–1.55	Langer
LGA (large for gestational age)	No treatment GDM vs. control	3.28	2.53–3.67	Langer
	Treatment GDM vs. control	1.06	0.81–1.38	Langer

Macrosomia Management in GDM

Table 2 shows an overview of data from studies on interventions related to macrosomia incidence in GDM (Langer et al., 2005; Horvath et al., 2010).

Herbst (2005) provided data on direct complications related to macrosomia. 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 cesarean delivery, and expectant treatment (**Table 3**).

Mortality outcomes were based on the study by Mitanchez (2010) who evaluated the risks of perinatal complications in infants born to mothers with treated or untreated GDM, including also risk of death.

Most of the costing data were derived from the studies by Herbst (2005), Ohno et al. (2011). In case of lack of information

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%

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 cesarean 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 (Ohno et al., 2011). 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%.

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_pretermdelivery	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

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.

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 (Indexmundi, 2014; www.indexmundi.com). In case of a GDM incidence rate of 5.5% (Zawiejska et al., 2014), this represents an annual number of GDM cases of 236 139 in the US. With a cost difference between normal pregnancy/delivery

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	$9,363
20%	$1,474,020,507	$2,211,030,761
Cost complications baby		
−20%	$5,444	$10,161
20%	$1,285,536,028	$2,399,515,240
Cost complications mother		
	$7,043	$8,563
	$1,663,105,770	$2,021,945,498

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, and will be of use 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.

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 (Jiwani et al., 2012; Sacks et al., 2012).

Relevance and Applicability of this Framework

Maternal BMI, nutritional status and dietary intake are the main determinants of fetal growth as well as 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 (Hunsberger et al., 2010). 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 (Mulla et al., 2010).

A limitation of this modeling approach lies in the lack of randomized trial evidence on targeted lifestyle interventions in pregnancy and their effect on birth outcomes (Balaji et al., 2014; Briley et al., 2014). 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 (Liu et al., 2012; Black et al., 2013; Li et al., 2013; Shi et al., 2014), 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 (Catalano, 2003; Roseboom and Watson, 2012), 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 (Thangaratinam et al., 2012). Evidence from observational studies and clinical trials indicates that dietary energy intake and the source of energy influences glucose metabolism and insulin responses (Hu et al., 2001; Galgani et al., 2008). High fat diets, likely to be unbalanced in their macronutrient composition, have been demonstrated to increase the risk for GDM recurrence in future pregnancies (Moses et al., 1997). 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 (Romon et al., 2001) indicating the significance of sufficient carbohydrate intake during pregnancy. 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 (Ley et al., 2011). 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 (Murrin et al., 2013). 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 (McGowan and McAuliffe, 2010; Tzanetakou et al., 2011). 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 (Bellamy et al., 2009; Jiwani et al., 2012).

A review by Henry and Beischer (1991) provides similar results. Using life table techniques, 17 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 (Sparano et al., 2013).

A recent prospective study, conducted in China, examined the risk factors and long-term health consequences of macrosomia (Gu et al., 2012). Using a population sample of 21 315 mother-child pairs, the children were prospectively followed and assessed for obesity 7 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 (Arslanian and Suprasongsin, 1996; Young-Hyman et al., 2001). 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 (Finkelstein et al., 2014).

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 (Savona-Ventura and Chircop, 2003) demonstrated that high birth weight is an important correlate for the subsequent development of GDM in later life. 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 (Boney et al., 2005). 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 birth 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.

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frontiers in Pharmacology

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Assessing the impact of dietary habits on health-related quality of life requires contextual measurement tools

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The increase of non-communicable diseases at all ages has fostered the general concern for sustaining population health worldwide. Unhealthy lifestyles and dietary habits impacting physical and psycho-social health are well known risk factors for developing life threatening diseases. Identifying the determinants of quality of life is an important task from a Public Health perspective. Consumer-Reported Outcome measures of health-related quality of life (HRQoL) are becoming increasingly necessary and relevant in the field of nutrition. However, quality of life questionnaires are seldom used in the nutrition field. We conducted a scientific literature search to find out the questionnaires used to determine the association between dietary habits and quality of life. A total of 13 studies were eligible for inclusion. Across these studies the short form-36, a generic (non-disease specific) HRQoL measurement instrument was the most widely used. However, generic measures may have limited content validity in the context of dietary habits interventions. We recommend additional contextual diet-specific HRQoL measures are also needed for evaluating the impact of diet habits on daily life functioning and well-being.

Keywords: dietary habits, quality of life, health outcome measures, general population, review

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Introduction

Although life expectancy has increased notably in the last years, non-communicable diseases at all ages are increasingly threatening the general population health globally. As people are living longer, policies and programs that enact "active aging" are a necessity. Measuring health-related quality of life (HRQoL) is related to the subjective perception of individuals' health and well-being in relation to its social and cultural environment (Testa and Simonson, 1996). Several factors are well-known determinants of HRQoL (Corica et al., 2008; Guitérrez-Bedmar et al., 2009; Serrano-Aguilar et al., 2009). Diet, together with other aspects of daily life such as physical activity and the relation with the environment, plays a crucial role in our state of physical and mental health.

Self-perceived health status is a simple but effective indicator of overall health status and a useful tool to inform about the care needs and the organization of prevention programs (Guyatt et al., 2007). HRQoL questionnaires are an efficient way of gathering data about people's daily functioning and psycho-social well-being. Also, health status measures have been shown to be a powerful predictor for chronic diseases and mortality over the long term in clinical practice (Wannamethee and Shapher, 1991).

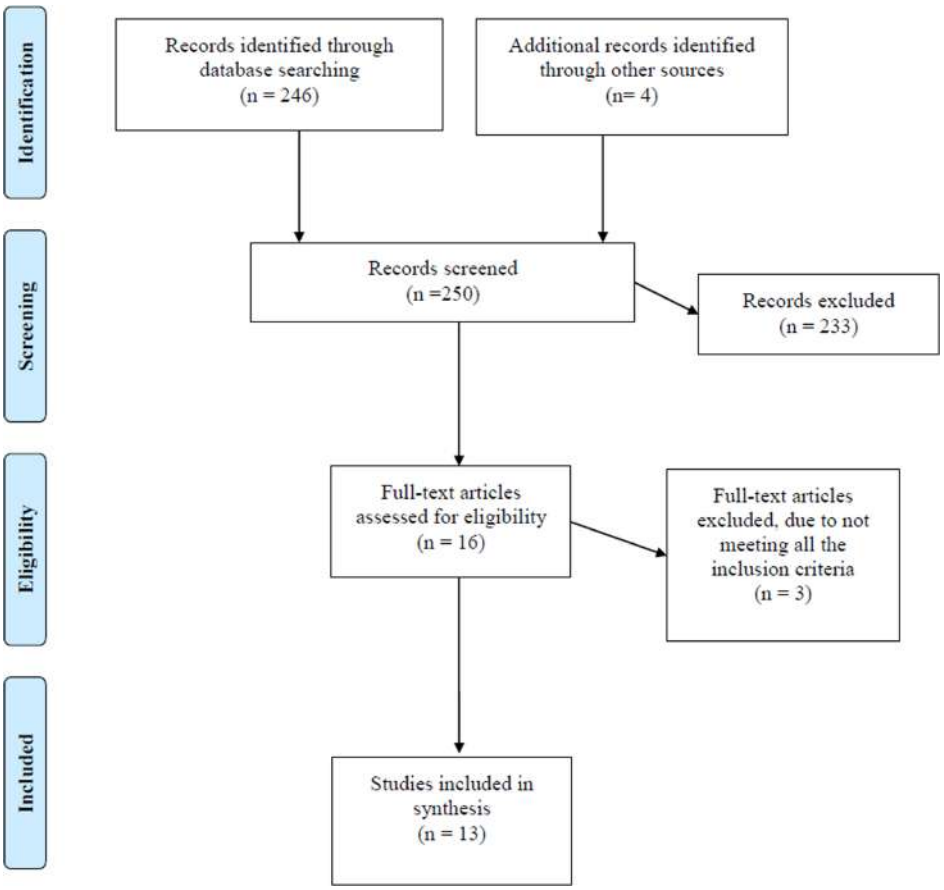

FIGURE 1 | Flow diagram of the review process.

It is now well established that nutrition influences outcomes in patient populations (Barr and Schumacher, 2003a,b), but few studies have assessed the relationship between HRQoL and dietary habits in the general population. Among them, the most used instrument to assess quality of life is the short form-36 (SF-36) Health Survey. However, generic health status measures may have limited content validity in the context of dietary habits interventions. So, our aim was to conduct a review to find out in the scientific literature the questionnaires used to determine the association between dietary habits and quality of life.

Materials and Methods

The literature search was conducted in Medline, using combinations of the following terms: "diet," "quality of life," and "questionnaires," including MESH-terms. In total 246 articles were selected.

The studies were evaluated applying the following inclusion criteria: (a) studies conducted exclusively in the general population (b) human studies (c) studies written in English (d) studies which used a validated assessment method and (e) studies published in the last 10 years.

After initial review of titles and abstracts, 12 articles appeared to be potentially relevant, and we attempted to obtain them in full-text version. The literature lists in the selected papers were checked. We selected by handsearching four studies from this literature that met the inclusion criteria. Of these 16 potentially eligible articles, three were excluded because they did not meet all eligibility criteria. Finally 13 articles were included in this study (**Figure 1**).

Results

The descriptive characteristics of the articles selected are reported in **Table 1**. From the 13 studies, six were cross-sectional, two randomized clinical trials, six cohort studies, and two validation studies of nutrition-specific tools for HRQoL assessment. The study samples included mostly adult populations except Costarelli et al. (2013) and Wu et al. (2012), which were conducted in young populations (10–16 years old).

The majority of the studies used the SF-36 for assessing quality of life. The exceptions were the two studies conducted in adolescent populations: one study conducted by Costarelli used a specific version of a generic questionnaire for young people: EQ-5D-Y (youth), and the other study (Wu et al., 2012) used the KIDSCREEN-27 questionnaire, an instrument to assess subjective health and well-being applicable for healthy and chronically ill children and adolescents aged from 8 to 18 years. Two other

TABLE 1 | Characteristics of included studies ($n = 13$).

Authors	Study	Design	Country	Sample characteristics (group size, *n*; age, years; gender)	Quality of life instrument used
Duncan et al. (2014)	10,000 Steps cohort	Cross-sectional	Australia	$n = 10,478$; ≥18 years; 70.5% women	CDC Healthy Days Instrument
Berendsen et al. (2013)	NU-Age project	RCT	European Consortium	$n = 1,250$; 65–80 years	SF-36
Ruano et al. (2013)	SUN project	Cohort	Spain	$n = 11,128$; >21 years	SF-36
Germain et al. (2013)	SU.VI.MAX trial	Cohort	France	$n = 3,005$; 45–65 years; 67.7% women	SF-36
Uritani et al. (2013)		RCT	Japan	$n = 114$; women 40–74 years	SF-36
Costarelli et al. (2013)		Cross-sectional	Greece	$n = 359$; 13–16 years	KIDSCREEN-27
Henríquez Sánchez et al. (2012)	SUN project	Cohort	Spain	$n = 11,015$; >21 years	SF-36
Wu et al. (2012)	REAL Kids Alberta	Cross-sectional	Alberta (Canada)	$n = 3421$; 10–11 years	EQ-5D-Y (youth)
Muñoz et al. (2009)		Cross-sectional	Girona (Spain)	$n = 7,145$; 25–74 years; 3,697 women	SF-12
Bonaccio et al. (2013)	Moli-Sani project	Cross-sectional	Italy	$n = 16,937$; ≥35 years; 48.4% men	SF-36
Kimura et al. (2009)		Cross-sectional	Japan	$n = 689$; ≥65 years; 401 women	QOL
Schünemann et al. (2010)		Validation study	Italy	$n = 128$; 20–65 years; 35.9% men	QUALCIBO
Guyonnet et al. (2008)		Validation study	France	$n = 197$; 20–65 years; 64% women	FBA

studies used a specific tool for assessing HRQoL: the CDC Healthy Days instrument in the study conducted by Duncan et al. (2014), and the quantitative HRQoL for old people living in the community, in the study conducted by Kimura et al. (2009).

We identified only two nutrition-specific instruments: the Food Benefits Assessment (FBA; Guyonnet et al., 2008) and the Qualcibo questionnaire (Schünemann et al., 2010).

Discussion

This review, designed to find out which instrument was mostly used to determine quality of life in relation to dietary habits, revealed that there are few studies that have been conducted to determine if the adherence to a specific dietary pattern could have a positive or negative influence on HRQoL in the general population. The large majority of studies regarding nutrition and quality of life have been performed in a clinical setting (Katcher et al., 2010; Cash et al., 2012) and the SF-36 was the most widely used measurement tool in this setting (Imayama et al., 2011; Villareal et al., 2011; Xu et al., 2012).

To our knowledge only two specific instruments have been developed to determine specifically the impact of diet on HRQoL in the general population, but we did not find any publication regarding their practical application, possibly because their validation is still in progress. Our results are in concordance with a recent systematic review conducted by Carson et al. (2014) regarding the effects of dietary interventions to promote weight loss on quality of life. One of the questionnaires is The FBA developed by Guyonnet et al. (2008), this questionnaire contains 41 questions that measure the impact of daily diet on eight dimensions of HRQoL, as perceived by subjects: vitality (10 items), digestive comfort (nine items), disease prevention (six items), well-being (six items), aesthetics (five items), physical appearance (three), snacking (two items), and pleasure (two items). The 41 items of the questionnaire showed good internal consistency reliability (Cronbach's $\alpha = 0.79$ to 0.91) and reproducibility. Intraclass correlation coefficient (ICC) scores exceeded the 0.70 threshold for all dimensions. When comparing FBA dimensions with SF-36 to determine the concurrent validity of the questionnaire, the Spearman correlation coefficients ranged from 0.02 (snacking) to 0.83 (well-being). No floor or ceiling effects were detected. The FBA's sensitivity over time needs to be determined in further long-term studies, as acknowledged by the authors.

The other nutrition-specific instrument most recently developed is the Qualcibo questionnaire initially validated for Italian population by Schünemann et al. (2010). It contains 29 items across five domains to assess quality of life related to nutrition and other aspects of food intake: Healthy lifestyle ($n = 10$ items), symptoms ($n = 6$ items), sensations ($n = 6$ items), social and role function ($n = 4$ items), and taste ($n = 3$ items). The Qualcibo questionnaire still needs further longitudinal construct validity and responsiveness assessment, since the authors only performed cross-sectional validation.

The following studies illustrate that generic, disease-specific and nutrition-specific questionnaires can provide valuable insights on the impact on general quality of life, as long as the measurement tool is applicable to the context and the research question of interest.

The CDC's Healthy Days instrument was used in a large cross-sectional on-line survey in members of the web-based 10,000 Steps project physical activity promotion initiative (www.10000steps.org.au). The study objective was to evaluate the HRQoL impact of several lifestyle behaviors, including diet (Duncan et al., 2014). The assessment of dietary behaviors included consumption of daily fruit and vegetables, soft drinks and fast foods. Poor dietary behaviors, as well as smoking, lower levels of physical activity, higher sitting time, and poor sleep behaviors, were shown to be associated with poor self-rated health and frequent unhealthy days.

In the 2001–2004 National Health and Nutrition Examination Survey, the Healthy Days questions were used to compare the impact of hypertension on general HRQoL in participants with and without hypertension (Hayes et al., 2008). A higher number of unhealthy days were reported by the respondents with hypertension.

The choice of the type of questionnaire should be based on the specific context and purpose of the study. For example, if the purpose is to compare the health status of healthy lifestyle and different diseases, the non-disease specific SF-36 is recommendable. If the purpose is to generate data that will allow to determine utilities for calculating Quality Adjusted Life Years, generic preference-based measures are recommended (e.g., EQ-5D, SF-6D, Health Utility Index; Walters and Brazier, 2003; Cruz et al., 2011).

To deepen the understanding of the impact of healthy as well as unhealthy dietary habits, we propose to start with reviewing the appropriateness of the few available nutrition-specific questionnaires for the specific purpose of your study, and search for other available measures to fill the potential contextual gaps, e.g., for measuring symptoms, (dis)satisfaction with (un)healthy diet intervention, or sleep quality.

Our study has some limitations. We limited our detailed review to those articles available in open access, so we could have missed other HRQoL instruments not available in a free format. We also limited our search to articles published in the last 10 years. We excluded articles not conducted in the general population. Given the ambiguity of the term general population, this may have led us to skip some studies in our search.

Conclusion

From a Public Health perspective it is an important but challenging task to measure the HRQoL effects of food habits within the general population. The choice of type of questionnaires depends on the specific research question to be answered. To our knowledge only two nutrition-specific instruments have been developed to determine the impact of nutrition in the general population. Additional measurement tools are needed to explore in more depth the associations between dietary habits and their impact on population health outcomes.

Author Contributions

CR and DD developed the study design and drafted the manuscript. LS provided guidance on analysis and data interpretation. All authors provided final approval of the manuscript.

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Nutrition and health technology assessment: when two worlds meet

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There is a growing recognition that nutrition may have a positive impact on public health and that it may reduce medical expenditures. Yet, such claims need to be substantiated by evidence. This evidence could be delivered by health technology assessment (HTA), which can be thought of as the evaluation of technologies for clinical effectiveness, cost-effectiveness, and ethical, legal, and social impacts. The application of HTA to the field of "nutrition interventions" is recent. So far, HTA and nutrition have represented two worlds far apart in many respects. This contribution, roughly, addresses the following issues: is there a need for HTAs in the field of nutrition, what would such HTAs look like, and how can the results coming from these HTAs optimally aid policy making?

In essence, HTAs of nutrition have much of the same basic principles and structure as HTAs of "classical" health care treatments. Nevertheless, there are challenges to rigorous HTAs of nutrition interventions, for various reasons. To mention a few: the evidence base for nutrition interventions is less well developed than that for many health care treatments. Furthermore, it is a matter of debate which outcome measures should be used in HTAs of nutrition. For example, one may argue that nutrition not only has health effects, but also effects that are not captured by traditional health-related quality of life measures (e.g., the pleasure of eating, effects relating to ease of use, or effects on well-being).

HTAs in the field of nutrition may deliver information valuable to a wide range of stakeholders, including consumers/patients, health professionals, hospital administrators, insurers, and decision makers. The results of HTAs are typically used in making treatment guidelines, in informing decisions about reimbursement or about public health campaigns, etc. Yet, it is uncertain how the results of HTAs of nutrition can be used optimally. For example, would it be possible to summarize the results of a HTA in a single ratio (such as costs per quality-adjusted life-year gained) and then to either approve or reject the intervention based on this ratio, compared to a certain threshold? Apart from that, in the field of nutrition, it is typically not about reimbursement of a technology. Related to this, it is important that the message from HTAs of nutrition is brought to a range of stakeholders including the general population and that these HTAs are tailored to the decision-making context.

To conclude, a growing need is felt for HTA-type evaluations of nutrition, which are sparse these days. Little thought has been given to developing an optimal methodology for HTAs of nutrition and to how its results should be integrated into policy making. Further work in these areas would stimulate the development of nutrition interventions that yield a gain in societal welfare. To achieve this, the two worlds of HTA and nutrition need to be brought together.

Keywords: health technology assessment, nutrition, nutrition economics, cost-effectiveness, economic evaluation

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INTRODUCTION

Over the last decades, the pattern of disease shifted from acute diseases to chronic diseases, which are of long duration and generally slow progression. The main types of chronic diseases, also known as non-communicable diseases (NCDs), are cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes. NCDs account for 38 million deaths each year (World Health Organization, 2014). One of the risk factors of NCDs is an unhealthy diet, next to other behavioral risk factors (such as tobacco use) and metabolic/physiological risk factors.

Due to developments like these, there is a growing recognition of the positive impact that nutrition may have on health. This holds for many diseases. To give one example, it has been calculated that 25% of all cancers could be prevented by the right nutrition, together with sufficient physical activity and a healthy body weight (World Cancer Research Fund and American Institute for Cancer Research, 2007). Accordingly, it has been recognized that diet changes have the potential to reduce medical expenditures by considerable amounts. For example, it has been calculated in the United States that a permanent reduction of 100 kilocalories in daily intake would result in savings of related medical costs of 58 billion dollars annually, as it would eliminate some 70 million cases of obesity or overweight (Dall et al., 2009). In this context, it should be noted that nutrition cannot only be effective in the long-term prevention of diseases. It may also have a role in the management of specific disease areas. For example, food supplements or dietary modifications may lead to cognitive improvement (or at least a delayed decline) in patients with early Alzheimer's disease (Shah, 2013; Swaminathan and Jicha, 2014). To give another example, probiotics have been demonstrated to be beneficial in preventing acute upper respiratory tract infections and in reducing the duration of illness episodes (King et al., 2014; Hao et al., 2015). Finally, nutrition interventions may also have positive effects in the short term: for example, oral nutritional supplements in malnourished hospitalized patients have repeatedly been shown to be associated with a reduced length of hospital stay and thus cost savings (Freijer et al., 2014; Lakdawalla et al., 2014; Walzer et al., 2014).

So, on the whole, it seems that nutrition can have many positive societal effects, in terms of public health and health care costs. Yet, however encouraging this observation is, such claims need to be substantiated by evidence on its positive outcomes, in relation to the additional cost (or: savings) that it may bring about. A discipline that seems well suited to deliver this kind of evidence is called health technology assessment (HTA). HTA has developed strongly over the last decades. From the beginning its intent was to consider the social impact of medical technologies, in order to enable optimal decisions regarding the use and reimbursement of such technologies. HTA has been described as the evaluation of high-priority technologies for efficacy, safety, cost-effectiveness, and current and potential economic, ethical, legal, and social impacts (Perry and Eliastam, 1981). So, HTA takes a multidisciplinary approach, yet assessing the economic impact of health technologies—that is, the balance between costs and (health) benefits—has prevailed in practice. In this respect, the term nutrition economics (as a novel branch of health economics) has become increasingly popular in the field of nutrition (Lenoir-Wijnkoop et al., 2011, 2012; Koponen et al., 2012). In the context of this paper, the term HTA will be used, as it intends to take a broad look at the assessment of nutrition interventions, extending beyond economic impacts alone. But also here, the focus will be on the economic evaluation of nutritional interventions.

Information derived from HTAs has played a growing role in health care decision-making. HTA offers a source of information needed by, for example, policymakers in formulating regulations, by industry in developing products, by health professionals in treating and serving patients, and by consumers in making personal health decisions. It is in line with current trends of evidence-based medicine, where the evidence is not limited to evidence on "clinical" effectiveness only, and growing (financial and other) constraints on the health care sector. To be funded from public funds, interventions increasingly need to have demonstrated safety, effectiveness, and value for money.

The application of HTA to the field of nutrition is recent. That is, from its origin, HTA has mainly been applied to "classical" health care treatments, especially to pharmaceutical interventions and high-technology, expensive treatments such as organ transplantation, kidney dialysis, et cetera. Recently, the conviction has been growing that HTA should also be applied to "nutrition interventions." Early examples of HTAs in the field of nutrition include HTAs of home parenteral nutrition and HTAs of nutrition interventions targeting disease-related malnutrition. However, nutrition does not parallel health care treatments. Consider that, as will be further explained below, there are many differences for example regarding the "technology" itself, the target population, the policy context, and so on. Consequently, HTAs of nutrition are not necessarily identical to HTAs of health care treatments.

To shed light on some of the questions surrounding the application of HTA to the field of nutrition, this contribution will address the following main questions:

- Is there a need for HTAs in the field of nutrition? Can nutrition interventions be regarded as "health technologies"?
- What would a HTA in the field of nutrition look like, compared to HTAs of "classical" health care interventions?
- Does a HTA in the field of nutrition require other outcome measures, compared to HTAs of "classical" health care interventions? Would the concept of quality of life be a suitable outcome measure?
- How can the results coming from these HTAs optimally aid policy making?

THE NEED FOR HTAS IN THE FIELD OF NUTRITION

Like mentioned above, HTAs have typically focused on "classical" health care treatments, especially on pharmaceuticals and high-technology, expensive treatments. That is, technologies that are used in patients with a diagnosis, that are prescribed by a doctor, and frequently have a direct, observable effect. Nutrition interventions clearly need to be distinguished from health care

treatments, for several reasons. They have a different working mechanism: as noted by de Vos et al. (2006), whereas drugs generally contain a single effective component that is specific and only has one target site in the body (producing a large effect), foods consist of a variety of components and can have effects on multiple targets (usually small effects). Furthermore, foods often sort an effect on the long-term, and finally, they are used (mostly on the individual's own initiative) not only for health purposes, but for other reasons as well (i.e., as a means to stay alive, to satisfy hunger, for pleasure). In addition, foods are consumed every day throughout life, whereas health care treatments are usually required for a short period of time. Finally, to be successful, nutrition interventions often require a change of habits. All this is further complicated by the fact that nutrition covers a wide range of food categories: from conventional food, to functional food, to infant food, to (enteral and parenteral) medical nutrition. So, at least they should be seen as diverse and atypical health technologies.

Nevertheless, there is a need for HTAs in the field of nutrition. Classical HTAs originated from the need that was felt to support decisions regarding the introduction of a technology to the market, reimbursement from the collective insurance, adoption in treatment guidelines, etc. HTAs in nutrition may deliver information that may be valuable to consumers/patients (who have to decide on buying a food product, the costs of which they have to bear themselves), to health professionals (who decide on prescribing of medical nutrition for example), to insurers (who may consider to reimburse functional foods for example) and to decision makers (who are responsible for investing in public educational campaigns and for regulating processes related to food labeling and health claims). This shows that HTA in nutrition is a broad field, which is also shown by the diversity of the subjects covered. These may range from studies of micronutrient deficiencies and malnutrition, to studies of dietary improvements, to studies of functional foods (Gyles et al., 2012). To use another categorization showing the variety of the area of interest: HTAs in nutrition may study subjects as diverse as interventions at the individual level (e.g., advice on diet), interventions at the group level (e.g., group education in schools), and interventions at the population level (e.g., taxes on unhealthy foods).

HTAS OF NUTRITION

Having said this, one may wonder what a HTA in nutrition would look like, compared to HTAs of "classical" health care interventions. Is there a need to use adapted techniques, or would regular HTA methods, as they have been developed and refined over the last decades, suffice?

As it will be argued below, in essence, HTAs of nutrition have much of the same basic principles and structure as HTAs of health care, just like the main purpose of those HTAs is the same (i.e., to inform technology-related policy making in health care, against the background of scarce resources). In each field of interest, HTA will basically follow the same steps. Consider for example the 10 basic steps of HTA set out by Goodman and Ahn (1999): (1) Identify assessment topics; (2) Specify the assessment problem; (3) Determine locus of assessment; (4) Retrieve evidence; (5) Collect new primary data (as appropriate); (6) Interpret evidence; (7) Synthesize/consolidate evidence; (8) Formulate findings and recommendations; (9) Disseminate findings and recommendations; (10) Monitor impact.

Nevertheless, there are challenges to rigorous HTAs of nutrition interventions, for various reasons. To mention a few: assessment of nutrition interventions has traditionally mainly relied on non-experimental methods, such as cohort studies, case-control studies, or surveys, as randomized controlled trials (RCTs) are ill-suited for the evaluation of nutrition (Heaney, 2008). So, its evidence base is less well developed than that for many health care treatments, lacking high-quality evidence of cause and effect. Furthermore, also given the absence of RCTs, confounding factors may be present in HTAs of nutrition. This is because people may change their behaviors in other ways as well (as part of an overall lifestyle change), apart from just starting to consume a food product. Next, there is less practical HTA experience in nutrition than in other technologies, such as drugs. Finally, it is a matter of debate which outcome measures can and should be used in HTAs of nutrition, which is the focus of the next section.

So, to conclude, there are specific demands to HTAs of nutrition, which may require such HTAs to move away from traditional HTA methods. Importantly, however, this does not only apply to nutrition, but to other areas as well: for example, the evaluation of public health interventions and long-term (palliative) care services may also raise additional methodological challenges, as has been noted in the literature (Gomes et al., 2009; Weatherly et al., 2009). HTAs of nutrition interventions can benefit from developments in these other areas (and *vice versa*), given that the methodological issues partly coincide with each other.

OUTCOME MEASURES USED IN HTAS OF NUTRITION

One of the questions is whether HTAs in the field of nutrition require other outcome measures, compared to HTAs of "classical" health care interventions? In the field of HTA, outcome measures have been developed, to capture the effects of health technologies on patients' length of life (mortality) and on quality of life. Especially, a large interest has been dedicated to health-related quality of life (HRQoL). HRQoL has been defined as "the physical, psychological, and social domains of health, seen as distinct areas (or domains) that are influenced by a person's experiences, beliefs, expectations, and perceptions" (Testa and Simonson, 1996). So, HRQoL is a multidimensional construct, encompassing physical, emotional, and social domains. Furthermore, it is about the subjective perception of the relevance and importance of health states to the individual.

Would the concept of HRQoL be a suitable outcome measure in nutrition? To answer this question, a number of observations are worth noting. First, nutrition has effects that are indeed relevant to the patient and that may be captured by measures of HRQoL. Quality-adjusted life-years (QALY), a common outcome measure in HTA, can be used. This has been done, for example, in studies on medical nutrition (Freijer et al., 2014) and in studies on public health interventions, aimed at decreasing fat or sodium

intake (Smith-Spangler et al., 2010; Bos et al., 2011). This leaves unaffected that, in the design of a HTA study, measures of HRQoL may be combined with other outcome measures, such as biological and physiological variables (i.e., changes in cell, organ and organ system function) and traditional nutritional outcomes such as energy intake, weight gain, and BMI. For example, one may think of the impact of prebiotic and probiotic foods on the improvement of gut flora, which has attracted much interest recently. Furthermore, it must be realized that nutrition may have an effect only over a long time span, which will have to be taken into account when designing and performing HTAs. Yet, this is not only true for nutrition, it does also apply to some (preventive) health care technologies. So, in sum, if a nutrition intervention aims to increase health, HRQoL measures such as the QALY may be perfectly suitable. However, nutrition may have effects that are not captured by traditional HRQoL measures. We may think of taste, the pleasure of eating, effects relating to comfort or ease of use, effects on well-being or happiness, or intermediate effects on health such as a quicker recovery from surgery or quicker recuperation time needed before receiving a next treatment. This may give nutrition interventions a comparative advantage, ceteris paribus, relative to health care treatments. For example, it may be more pleasurable to eat margarine, yogurt, etc. than to take a drug, just like people may prefer taking a drug to surgery. If an intervention also aims to bring such other "broader" positive effects (other than HRQoL), appropriate outcome measures must be sought to capture the full benefits of nutrition.

Obviously, people attach importance to the health outcomes of health care treatments (and health systems). Yet, there is evidence now that people also care about the processes that precede health outcomes, irrespective of whether they affect health. This has been labeled "process utility" (i.e., utility derived from processes; Donaldson and Shackley, 1997; Ratcliffe and Buxton, 1999; Brennan and Dixon, 2013). Characteristics relating to the process of care may include factors such as invasiveness of the treatment, location and context of the treatment provided, continuity of staff, being treated with dignity, and level of autonomy experienced by the patient. To achieve optimal resource allocation, HTAs should take into account utility resulting from the process of care, next to health gains. This is especially relevant when the field of interest is so broad as to encompass health care interventions (which may range from curative care to preventative care, to comfort care and palliative care) and nutrition interventions.

Finally, it should be recognized that nutrition can have effects on others than the patient/consumer him or herself, which should be taken into consideration in HTA studies (like it is increasingly done in HTAs of health care treatments). Currently, there is only limited evidence on this. One study, for example, evaluated the impact of gastrostomy tube feeding on the HRQoL of carers of children with cerebral palsy. The study reported a significant improvement in the carers' HRQoL after insertion of a gastrostomy feeding tube, coupled with a significant reduction in feeding times (Sullivan et al., 2004). A recent RCT in newborns with functional gastrointestinal disorders showed that daily administration of a probiotic decreased the onset of gastrointestinal disorders, reduced daily crying time, and led to overall cost savings, by reducing both health care use and lost parental working days (Indrio et al., 2014). These examples highlight that HTAs should take into account effects on others, as nutrition interventions may alleviate the burden on caregivers, improve their HRQoL, avoid productivity losses, and be associated with cost savings.

PUTTING THE EVIDENCE OF HTAS OF NUTRITION INTO PRACTICE

The result of any HTA is an assessment of the value (for money) of a health technology. This may, for example, involve the economic costs and clinical effectiveness of a technology, but also ethical and legal pros and cons, the social impact, etc. The results of HTAs are typically used in making treatment guidelines, in informing decisions about reimbursement (in- or exclusion from the benefits package) or about public health campaigns, etc.

The results of a conventional HTA may be summarized in a so-called incremental cost-effectiveness ratio (ICER), which expresses the extra costs required to achieve one additional unit of benefit, such as costs per life-year gained or costs per QALY gained. When the results of an HTA are being used in this way, some threshold would be practical beyond which the technology will not be recommended (approved for funding). However, in no single country, an absolute threshold is being used by decision-makers. Yet, in practice, the chance of rejection increases with decreasing cost-effectiveness. For example, in the UK, it seems that technologies costing £40,000 per QALY have a 50% chance of being rejected (75% at £52,000/QALY; 25% at £27,000/QALY; Dakin et al., 2014). Apparently, it is difficult to fix a certain threshold, and apply it uniformly. There has been plenty of discussion about whether the outcomes should be valued differently for different areas of health care, for example life-threatening severe diseases, treatments targeted at children rather than older people, comfort care rather than curative care, rare diseases, diseases that can be attributed to the responsibility and choice of the individual, etc. (van de Wetering et al., 2014). This suggests that other arguments, most notably equity, play a role in decisions about recommending for or against a technology. Even within health care, we as a society seem to be willing to pay more (i.e., accept a higher threshold) for certain technologies (and disease areas) than for others. What about interventions in the field of nutrition? This is far from clear yet, but likely is related to the characteristics of the beneficiaries.

Furthermore, and perhaps more importantly, it may be reminded here that in the field of nutrition, it is typically not about reimbursement of a technology. Although there have been examples, food products are typically not reimbursed by a third-party payer, but instead paid for out-of-pocket by consumers. Related to this, especially in the area of nutrition, it is important that the message from HTA is brought to the general population (rather than mainly to health care providers or decision-makers). The public could be stimulated to make good food choices, as such, putting the results from HTA into practice. This may be challenging, because consumer food choices are affected by many different factors, including nutrition knowledge, sensory preferences, cost, availability and access to stores, cultural background, social environment, and food marketing

(Larson and Story, 2009). This is quite different from health care settings, where, roughly speaking, patients follow their doctor-prescribed regimen (even though the issue of non-compliance must not be underestimated). HTAs in nutrition should ideally take this into account. As a general note, it is worth mentioning here that HTAs of nutrition should target the information needs of different stakeholders, which may include both policy makers, hospital administrators, and the general public. Any HTA of nutrition should think about the following questions: who is the decision maker that needs to informed, which information is most relevant to this decision maker, and what is the decision making context?

CONCLUSION

This paper focused attention on HTA and nutrition, two worlds far apart in many respects so far. Increasingly, the need is felt for HTA-type evaluations of nutrition, which provide information relevant to a wide range of stakeholders, including consumers/patients, health professionals, hospital administrators, insurers, and decision makers. Yet, currently, such evaluations, delivering evidence on the social impact of nutrition, are sparse. Moreover, little thought has been given to developing an optimal methodology for HTAs of nutrition, that is, whether current HTA methods suffice or would need adaptation to capture the specific nature of nutrition. Then, a better understanding is required of how to optimally orient HTAs of nutrition to the needs of policy makers and how to integrate the results of these HTAs into policy making (e.g., what criteria can be used to decide for or against a certain nutrition intervention and where to draw the line between cost-effective and cost-ineffective nutrition interventions). Further work in all these areas would stimulate the development of nutrition interventions that generate positive effects on society's health, and that do so at a reasonable additional cost (or are even associated with cost savings). So, there is a potential gain in societal welfare. To achieve this, the two worlds of HTA and nutrition need to be brought together.

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Nutrition, a health technology that deserves increasing interest among HTA doers. A systematic review

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The increasing interest for evaluating indirect consequences of health care interventions and their interaction with patients' behavior have put the focus on health promotion interventions including nutrition and the need to measure and evaluate them.

Objective: In this review we have aimed to analyze current status of written and published reports on nutrition and nutrition interventions by HTA doers, how assessment has been approached and which metrics and designs have been proposed.

Methods: For that purpose, we searched the Center for Reviews and Dissemination databases (CRD) comprising the International Network of Agencies for HTA database (INAHTA), the database of effects (DARE) and the National Health Service Economic Evaluation Database (NHS EED). The words used include nutrition and nutrition interventions and there was no limit on data coverage. We complemented the search by manually seek for further reports on INAHTA's agencies webpages. We extracted the reports for their classification and analysis.

Results: We found 82 reports from different sources and after applying inclusion and exclusion criteria, we finally included 42. All the reports correspond to High income Countries (HiC) including agencies from Europe, North America and Oceania. The agencies or programs most represented correspond to the NIHR (UK) and AHRQ (USA). There were general reports around the role of functional foods and specific reports on the impact of establishing nutrition specific strategies in hospitals. 6 out of 42 analyzed the economic consequences of nutrition interventions and 4 reports were related to the methodologies used or the appliance of systematic review methods to the field of nutrition.

Conclusions: the reports included correspond to HiC while those HTA agencies established in Low and Middle Income countries (LMiC) have no reported or written activities on the role of nutrition and nutrition interventions. Retrieved reports written by HTA doers/producers confirm the use and utility of systematic reviews and economic analysis methods and its applicability for nutrition interventions. However, some measurements such as Quality Adjusted Life Years (QALY) need to be refined to better reflect the impact of these interventions.

Keywords: nutrition, Health Technology Assessment, health technology, decision making, public health interventions

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Health technology assessment (HTA) is a multidisciplinary field of knowledge that addresses the different consequences of health technologies both direct and indirect to health systems. It embraces the analysis of clinical issues, economic aspects, organizational, legal, social, cultural and ethical issues that one single or a group of technologies can generate. Classically HTA has evaluated drugs, medical devices, surgical procedures and companion diagnostics while public health interventions including vaccines have been sporadically assessed. Nevertheless, and according to the definition of health technology from the HTAi glossary (http://htaglossary.net/HomePage)[1] it is an intervention that may be used to promote health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation. It includes pharmaceuticals, devices, procedures and organizational systems used in health care. There is an increasing interest in evaluating public health interventions and its consequences on health and health care systems. This relates not only to the existing initiatives but to the metrics used in evaluating them in order to justify further interventions. In fact, an active group started writing different papers on the role of nutrition and especially its economic impact and the ways of measure nutrition interventions (Lenoir-Wijnkoop et al., 2011, 2012; Gyles et al., 2012). This initiative was further discussed by some members of the international society Health Technology Assessment international (HTAi) which led to the creation of an Interest Subgroup (ISG) in the society. Interest Subgroups are hubs for sharing international experiences and expertise among HTA users and producers worldwide. This newly created ISG on the Impact of Public Health interventions, special focus on Nutrition, on Health Outcomes Research and Measurement (INPHORM) aimed to create a critical mass for discussion and a neutral forum for individuals who are involved in the research, assessment and/or management of public health interventions and a special focus nutrition-related health states and socio-economic outcomes from a broad perspective, including the individual and the societal level. In order to analyze the current situation of HTA analysis in the field of nutrition a systematic overview of existing written reports of the International Network of Agencies for Health Technology Assessment (INAHTA) was proposed. INAHTA is a network of 55 HTA agencies that support health system decision making that affects over 1 billion people in 33 countries around the globe. With more than 2,100 staff and consultants working in the INAHTA network (http://www.inahta.org) and a common database coordinated and organized by the Center for Reviews and Dissemination (CRD) of the University of York, INAHTA is the biggest community of HTA doers/producers. On the other hand, the CRD databases are updated daily and provide decision-makers with access to: over 30,000 quality assessed systematic reviews; over 16,000 economic evaluations and over 13,000 summaries of completed and ongoing health technology assessments. The CRD is the biggest database of HTA reports in the world and includes not only the reports from INAHTA members but from other HTA doers.

[1]HTA glossary. Available online at: http://htaglossary.net/HomePage Accessed on January 2015.

Objective

To conduct a systematic review of the HTA reports that analyzed nutrition and nutrition interventions from the main HTA organizations and doers.

Methods

We searched the CRD databases comprising the International Network of Agencies for HTA database (INAHTA), the database of effects (DARE) and the National Health Service Economic Evaluation Database (NHS EED). They are updated daily and include more than 60,000 registries of systematic reviews, economic evaluations and HTA reports. The search was complemented with a hand search of the webpages of the agencies members of INAHTA (currently 55 agencies from 33 countries including hospital based HTA units). There was no limit of publication data, the languages that were included were as follows: Spanish, English, Italian, German, French and Portuguese. Inclusion criteria were: HTA reports, economic evaluations or systematic reviews that embrace nutrition and nutrition interventions and that were included in the CRD databases or were available in the INAHTA's agencies webpages. We did not exclude reports if written in other languages if they had a comprehensive abstract with sufficient information in the previously reported languages. The search was closed the 31st of January 2015. Exclusion criteria comprise reports that had at least no abstract in the mentioned languages, which were related to other type of interventions different to nutrition (although they collaterally cited nutrition) or that the abstract was insufficient to provide enough information and the report was written in languages different to the included ones. Inclusion and exclusion criteria were independently applied by both researchers and discrepancies were solved by consensus among them. Finally included reports were classified in three main blocks: methodological studies, studies of effectiveness and reports that include economic analysis. In the case of those studies that report economic evaluation, the perspective used (health system or societal) was analyzed. We also extracted data on publication date, language, HTA agency, country and setting.

Results

We retrieved 82 reports (see **Figure 1**) from different agencies, after the application of inclusion and exclusion criteria, we finally included 42 reports (see **Table 1**). Fifteen reports were excluded due to the no-existence of comprehensive abstract in the languages considered, 20 due to interventions considered different to nutrition, one report was duplicated (protocol and study results) and 4 were finally excluded due to insufficient information from abstract and impossibility to retrieve further information from the agencies' webpage. The 42 finally considered reports were produced by 16 agencies from 10 countries (Australia, France, Germany, The Netherlands, Norway, Spain, Sweden, Switzerland, UK and USA). The agencies that produced the highest number of reports, eight reports, was the Agency for Health Research and Quality

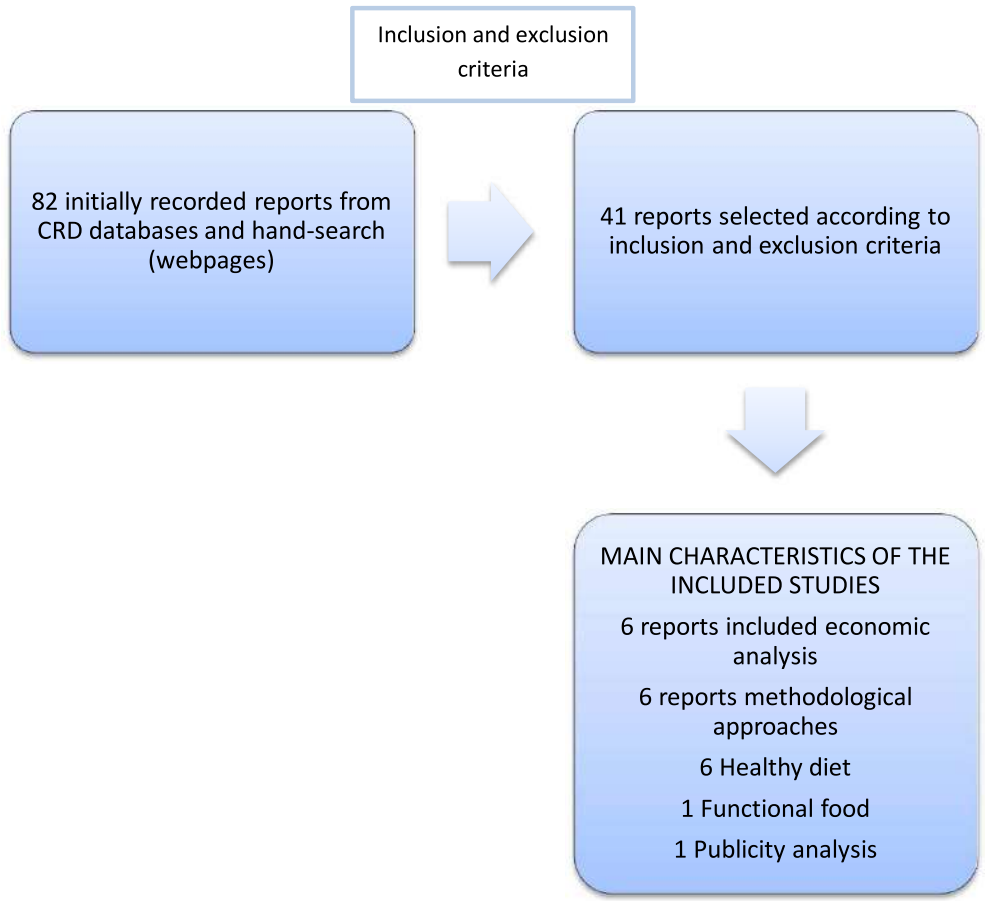

FIGURE 1 | Diagram of the performed search.

from the US administration and the National Institute for Health and Research (NIHR) Health Technology Assessment (HTA) Program from the UK with also eight published reports. Regarding the country with highest number of reports was the UK with 10 reports. According to World Banks'[2] classification all the countries with retrieved reports were classified as High Income Countries and all of them were OECD members (http://data.worldbank.org/about/country-and-lending-groups#High_income). Regarding the date of publication the period covered was 1994–2014. Thirty two reports out of 42 (76.2%) were published in the last 10 years, showing a trend to increase the number of publications around this topic. The highest number of publications was obtained in 2006 and 2009, the mean in the whole period covered was 2.1 and the mode 2.

Once the reports were analyzed we encountered as main characteristics that: 6 reports included analysis of cost-effectiveness, 6 reports methodological approaches, 6 around healthy diet, 1 functional food and 1 publicity analysis.

[2]World Bank's classification of countries and lending according to GNI per capita. Available online at: http://data.worldbank.org/about/country-and-lending-groups#High_income. [Accessed on January 2015].

Economic Studies

NIHR (Richards et al., 1997). This study compared home parenteral nutrition (HPN) and in-patient care, the main conclusions of the study in the economic side were related to cost minimization as it was stated by the authors the HPN treatment was cheaper than the alternative of in-patient care. The perspective use was health care system. Regarding the cost per QALY, two studies retrieved by this review showed that that the cost utility of treating younger patients was more favorable than older ones.

ZonMW (2006) on cost-effectiveness of nutritional screening and intervention in elderly subjects after hip fracture, performed an economic evaluation from societal perspective using a time horizon of 6 months the scale to calculate the QALY was the generic SF36 (Ware and Sherbourne, 1992). For the experimental intervention of the study, the authors performed a detailed micro-costing study that was performed using the activity-based costing method. According to authors the incremental cost-effectiveness ratios were determined through: (a) direct costs of the intervention (food supplement, consultation by dietician) per day reduction in total length-of-stay; (b) total societal costs (including medical costs, patient costs, and caregiver burden)

TABLE 1 | Characteristics of considered reports.

Agency	Title	Year	Outputs	Economic analysis
CADTH	Nutritional supplementation for patients with cancer: a review of the clinical effectiveness and guidelines	2014	Effectiveness	–
CADTH	Oral nutrition intake for the prevention of falls in older adults: clinical effectiveness and guidelines	2014	Effectiveness	–
SBU	Dietary treatment of obesity. A systematic review	2013	Benefits, risks, ethical considerations and Cost effectiveness	Cost effectiveness. Societal perspective
AHRQ	Interventions for feeding and nutrition in cerebral palsy	2013	Effectiveness	–
CEP	Nutrition during hospitalization for pediatric bronchiolitis	2013	Effectiveness	–
NIHR	Elemental nutrition for Crohn's disease	2013	Effectiveness and cost-effectiveness GRADE method for recommendations	Cost-minimization analysis and cost-effectiveness analysis.
NIHR	Adapting health promotion interventions to meet the needs of ethnic minority groups: mixed methods evidence synthesis	2012	Effectiveness	–
NOKC	The effectiveness of health promotion and preventive interventions on nutrition, physical activity, obesity and sexual health in children and adolescents	2012	Effectiveness	–
NIHR	The effectiveness of interventions to treat severe acute malnutrition in young children: a systematic review	2012	Effectiveness	–
GR	Guidelines for a healthy diet: the ecological perspective	2011	Sustainability	–
NIHR	CALORIES: A phase III, open, multicenter, randomized controlled trial comparing the clinical and cost-effectiveness of early nutritional support in critically ill patients via the parenteral vs. the enteral route	2011	Effectiveness and cost-effectiveness	Cost-effectiveness analysis from health and personal health services perspectives. Scale generic EQ5D
AHRQ	Nutritional research series: advancing the role of evidence-based reviews in nutrition research and applications Volume 2: issues and challenges in conducting systematic reviews to support development of nutrient reference values: workshop summary	2009	Methodology	–
AETMIS	Protein sparing modified fast diet: efficacy, safety and clinical use	2010	Efficacy, safety and clinical use	–
CADTH	Indirect calorimetry to measure energy requirements: a review of the guidelines and clinical effectiveness	2009	Clinical effectiveness	–
CADTH	n-3 lipids for patients on total parenteral nutrition: a review of the clinical and cost-effectiveness	2009	Clinical effectiveness and cost-effectiveness	Health care provider perspective, cost effectiveness
AHRQ	Nutritional research series: advancing the role of evidence-based reviews in nutrition research and applications. Volume 1: application of systematic review methodology to the field of nutrition	2009	Methodology	–

(Continued)

TABLE 1 | Continued

Agency	Title	Year	Outputs	Economic analysis
AHRQ	Nutritional research series: advancing the role of evidence-based reviews in nutrition research and applications. Volume 3: reporting of systematic reviews of micronutrients and health: a critical appraisal	2009	Methodology	–
IQWIG	Systematic guideline search and appraisal for the DMP module "Obesity"	2009	Methodology	–
GR	Healthy nutrition: a closer look at logos	2008	Effectiveness	–
AHRQ	Effectiveness and safety of vitamin D in relation to bone health	2007	Safety and effectiveness	–
AHRQ	Advancing the role of evidence-based reviews in nutrition research and science-based applications	2007	Methodology	–
NIHR	FOOD: a multicenter randomized trial evaluating feeding policies in patients admitted to hospital with a recent stroke	2006	Effectiveness	–
ZoNW	Cost-effectiveness of nutritional screening and intervention in elderly subjects after hip fracture	2006	Cost-effectiveness	Cost-effectiveness, societal perspective using a time horizon of 6 months. Scale generic SF36
Osteba	Development of an early detection and intervention system to prevent hospital undernourishment	2006	Effectiveness, prevention	–
GR	Guidelines for a healthy diet 2006	2006	Effectiveness	–
NICE	Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition	2006	Effectiveness	–
CEDIT	Nutrition support teams—systematic review, expert panel	2006	Effectiveness	–
GR	Food and nutrition in babies and young children. Review, expert panel	2006	Effectiveness	–
CEDIT	Nutrition support teams—preliminary report	2005	Effectiveness	–
ZONW	Activity, Lifestyle, and Nutrition and Therapy study (ALANT study)	2005	Effectiveness	–
AHRQ	Effects of omega-3 fatty acids on cardiovascular disease	2004	Effectiveness	–
CCE	Intravenous or nasogastric rapid rehydration for children with gastroenteritis?	2004	Effectiveness and safety	–
CCE	Assessing the effectiveness of total parenteral nutrition for simultaneous renal and pancreatic transplant patients	2003	Effectiveness	–
SBU	Geriatric care and treatment: a systematic compilation of existing scientific literature	2003	Effectiveness	–
AHRQ	Counseling to promote a healthy diet	2002	Effectiveness	–
CCE	"Open" vs. "closed" systems for enteral feeding	2002	Effectiveness and safety	–
CCE	Time to commencement of oral feeding following laryngectomy	2001	Effectiveness	–

(Continued)

TABLE 1 | Continued

Agency	Title	Year	Outputs	Economic analysis
ANAES	Care and monitoring of enteral access for enteral nutrition in adults in hospital and at home	2000	Effectiveness	–
TA-SWISS	Functional food	2000	Effectiveness	–
NIHR	Health promoting schools and health promotion in schools: two systematic reviews	1999	Effectiveness	–
NIHR	Home parenteral nutrition: a systematic review	1997	Effectiveness and cost-effectiveness	Health care perspective. Cost minimization and cost-utility
ANAES	Peri-surgical nutritional support (TPN or EN) in adults—consensus conference	1994	Effectiveness	–

per QALY. *Post-hoc* subgroup analyses were performed to study heterogeneity and related subgroup cost-effectiveness. The results of the study were finally published in 2013 (Wyers et al., 2013).

CADTH (2009) report on n-3 lipids for patients on total parenteral nutrition, is a review of the clinical and cost-effectiveness, the authors used the health care provider perspective due to the retrieved articles. They included a cost-benefit analysis and impact budget analysis. The limitations of the review were related to the scarce number of economic studies that addressed the theme.

NIHR (2011) (CALORIES). It is a pragmatic, open, multicenter, randomized controlled trial comparing the clinical and cost-effectiveness of early nutritional support in critically ill patients via the parenteral vs. the enteral route. It is one of the first approaches to perform an economic analysis of different nutritional strategies from data directly obtained from a randomized trials and micro-costing. The cost analysis will take a health and personal services perspective as per guidance from NICE (2004, 2007, 2013). The results of this trial have been partially reported in different articles (Harvey et al., 2014a,b) and they are planned to be finished by the end of 2015 (Available in: http://www.nets.nihr.ac.uk/projects/hta/075203 accessed on January 2015).

Tsertsvadze et al. (2013) is a non-finished commissioned report on the "Elemental nutrition for Crohn's disease." The systematic review includes an analysis of the effectiveness and cost-effectiveness and the authors plan to use GRADE method for the elaboration of recommendations. In the case of the economic analysis their approach will be cost-minimization analysis and cost-effectiveness analysis. The protocol can be consulted in: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0019/81820/PRO-13-08-01.pdf and the results are supposed to be published by mid 2015.

SBU (2013)[3]. This Swedish study around obesity and strategies to address the problem, performed by the Swedish Federal Office for HTA, tried to include all the domains of a HTA analysis. In the overview performed of health economic studies within the scope of this report, the authors indicated that there is a lack of well-executed studies relating to the cost-effectiveness of various types of dietary advice.

Methodological Studies

Maglione et al. (2007), Lichtenstein et al. (2009), Chung et al. (2009), Russell et al. (2009); see **Table 1**. The Agency for Healthcare Research and Quality's (AHRQ) is a governmental agency of the US that aims to produce evidence to make health care safer, of higher quality, more accessible, equitable, and affordable, and to work within the U.S. Department of Health and Human Services and with other partners to make sure that the evidence is understood and used. They produced a series of reports in order to guide any approach to the evaluation of nutrition research and its outcomes (Lichtenstein et al., 2008, 2009; Chung et al., 2009; Russell et al., 2009). They can be retrieved in: http://www.ahrq.gov/research/findings/evidence-based-reports/tr17-series.html They concluded that: (a) the methodological approach of "systematic reviews" is applicable to nutrition field; (b) there are problems of generalizability of well conducted studies to the overall population and appropriate interpretation and integration of scientific evidence from observational studies; (c) the reporting quality of SRs has improved 3 years after publication of SR reporting standards (since 2003), but the reporting of nutrition variables has not. Improved adherence to consensus methods and reporting standards should improve the utility of nutrition SRs.

IQWIG (2009). IQWIG is an organization commissioned by the German Federal Government to provide information on different topics for the German Healthcare System. They performed an analysis of the feasibility of the search on Clinical Practice Guidelines to inform and give recommendations regarding the role of nutrition and nutrition based interventions in obesity. They found that from the retrieved CPGs, RCT-based recommendations exist particularly in the care areas of nutrition therapy, physical activity therapy, behavioral therapy, pharmacotherapy and surgical therapy. In contrast, hardly any RCT-based recommendations could be identified

[3]SBU. (no 218/2013). Dietary treatment of obesity. A Systematic Review. Available online at: http://www.sbu.se/upload/Publikationer/Content1/1/Dietary_treatment_obesity.pdf

for the care aspects of diagnosis, monitoring and long-term weight maintenance, or for care coordination and quality indicators.

Discussion

Study Limitations

This is an overview of studies on nutrition and its consequences on health and wealth from the perspective of HTA and thus, it can be considered as a partial study of what is going on around nutrition and its possible impact on health and social care systems. In fact, we haven't considered the inclusion of broad databases such as Medline or EMBASE when looking for studies that address the effectiveness and cost-effectiveness of nutrition interventions. Nevertheless, searching the CRD is a recognized source when retrieving HTA reports or studies on effectiveness and cost-effectiveness (Royle and Waugh, 2003) from HTA doers and main agencies include their reports or articles in the three main databases comprised under the CRD interface (DARE, INAHTA, and NHS EED), but those produced by the British NIHR that are indexed in both the CRD and Medline (they appear under the name of Health Technology Assessment Journal). So any search that would have included Medline would have obtained duplicates for NIHR and no retrieves for other agencies but partial articles referring individual domains of full HTA reports indexed in the CRD. Moreover, in order to include all the possible reports, even those that were not indexed in the CRD, the authors sought for reports in the individual webpages of INAHTA agencies (HTA doers). HTA agencies or organizations, such as NICE or NIHR, no members of INAHTA also index their reports in the CRD databases.

Information Retrieval for Systematic Reviews in Nutrition Field and Its Validity for Decision Making Process

Most of the retrieved reports correspond to the analysis of the effectiveness of dietary interventions and their consequences from the perspective of clinical effectiveness, some of them concrete and focused on pathologies and one concrete clinical setting (see **Table 1**) and did not address a more broader approach related to overall consequences on health care and social systems. Nevertheless, those that have reported this broader perspective (IQWIG, 2009; SBU, 2013) found difficulties in covering domains that are usual in HTA analysis such as: legal, organizational, economic, ethical and social aspects. The reason was the lack of evidence (research studies) referred to these domains.

It is worth pointing out that the number of randomized studies published in the research field of dietary treatment and its consequences has grown exponentially since the mid-1990s (SBU, 2013). At least about a thousand randomized studies have been carried out by now, especially in the area of dietary treatment of obesity and diabetes type II. However, most of these have short follow-up times, small study populations, have not gauged compliance with the dietary advice given, or have been carried out in a manner which makes them difficult to interpret. Only a small number of studies compare the effects of two or more kinds of dietary advice with one another, and the majority of these have been published over the past decade. These findings are in accordance with what was previously described in another systematic review reported around the domain of health economics (Gyles et al., 2012).

Most striking as regards diet comparisons is the lack of outcomes important to patients, such as morbidity, death and quality of life. These issues are of key importance when performing studies that aim to address the validity of health interventions and the possibility of providing evidence to decision makers. Nonetheless, it is true that nutrition is an area of research in which there is a requirement of long-term follow-ups and well conducted studies that avoid biases in order to establish correlations to final outcomes and many studies included surrogate outcomes or endpoints (cholesterol, triglycerides, glucose amount or changes on Body Mass Index) as indicators of the effectiveness of the intervention (Lenoir-Wijnkoop et al., 2011).

Another concern related to the lack of studies that address the indirect consequences of nutrition interventions is the lack of quality of life measurements that include social and/or well-being statuses; in fact, there is a vivid debate on how to address this and well recognized public bodies like NICE and MRC are commissioning researches on this theme (Improving cross-sector comparisons: Beyond QALY, 2015)[4]. There are a number of proposed sector-specific tools available; in social care, the Adult Social Care Outcome Tool (ASCOT) has been developed for routine use in social services. In public health, there is no single measure, but there are a number of broader measures that could be used. These include measures of wellbeing such as the preference-weighted ICECAP capability index (Flynn et al., 2015), WEMWBS (Tennant et al., 2007) and the ONS-4 (Office for National Statistics, 2014). So, there is a need to define a broader instrument that allows the comparison among interventions on health or that affect health and well-being beyond the QALY concept and perhaps refine the currently applicable thresholds to many healthcare systems' interventions.

Finally, as it was described in the approach to methodology relevant to nutrition research reported by AHRQ, it is difficult to achieve an appropriate balance between well conducted studies and applicability at a broader population (external validity) and the integration of evidence obtained from well-conducted observational studies with long-term follow-up periods (internal validity). In this sense the implementation of new methods for systematic reviews elaboration that include clinical judgment such as GRADE (Guyatt et al., 2008) and its applicability to HTA (Ibargoyen-Roteta et al., 2010) and public health interventions (Weightman et al., 2005; Craig et al., 2011) could be helpful to improve the quality and the use of SRs regarding nutrition research and interventions.

[4]Improving cross-sector comparisons: Beyond QALY. MRC (2015). Available online at: http://www.mrc.ac.uk/funding/how-we-fund-research/highlight-notices/improving-cross-sector-comparisons-beyond-qaly/ [Accessed on April 2015].

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Cost-of-illness analysis reveals potential healthcare savings with reductions in type 2 diabetes and cardiovascular disease following recommended intakes of dietary fiber in Canada

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Background: Type 2 diabetes (T2D) and cardiovascular disease (CVD) are leading causes of mortality and two of the most costly diet-related ailments worldwide. Consumption of fiber-rich diets has been repeatedly associated with favorable impacts on these co-epidemics, however, the healthcare cost-related economic value of altered dietary fiber intakes remains poorly understood. In this study, we estimated the annual cost savings accruing to the Canadian healthcare system in association with reductions in T2D and CVD rates, separately, following increased intakes of dietary fiber by adults.

Methods: A three-step cost-of-illness analysis was conducted to identify the percentage of individuals expected to consume fiber-rich diets in Canada, estimate increased fiber intakes in relation to T2D and CVD reduction rates, and independently assess the potential annual savings in healthcare costs associated with the reductions in rates of these two epidemics. The economic model employed a sensitivity analysis of four scenarios (universal, optimistic, pessimistic, and very pessimistic) to cover a range of assumptions within each step.

Results: Non-trivial healthcare and related savings of CAD$35.9-$718.8 million in T2D costs and CAD$64.8 million–$1.3 billion in CVD costs were calculated under a scenario where cereal fiber was used to increase current intakes of dietary fiber to the recommended levels of 38 g per day for men and 25 g per day for women. Each 1 g per day increase in fiber consumption resulted in annual CAD$2.6 to $51.1 million savings for T2D and $4.6 to $92.1 million savings for CVD.

Conclusion: Findings of this analysis shed light on the economic value of optimal dietary fiber intakes. Strategies to increase consumers' general knowledge of the recommended intakes of dietary fiber, as part of healthy diet, and to facilitate stakeholder synergy are warranted to enable better management of healthcare and related costs associated with T2D and CVD in Canada.

Keywords: fiber consumption, type 2 diabetes, cardiovascular disease, economic benefits, healthcare cost saving, nutrition economics, public health

Abbreviations: CIHI, Canadian Institute for Health Information; CVD, cardiovascular disease; EBIC, Economic Burden of Illness in Canada; IOM, Institute of Medicine; NHEX, National Health Expenditure Trends; T2D, type 2 diabetes.

Introduction

Globally, the growing prevalence of type 2 diabetes (T2D) and CVD has been accompanied by escalating costs related to healthcare and society's loss of productivity, putting these two diet-related epidemics among the world's top public health policy priorities. Approximately 9% of adults around the world were diagnosed with diabetes in World Health Organization (2014), of which 90% had T2D, together with 4.9 million deaths and diabetes-related costs that reached US$612 billion. In Canada, the prevalence of diagnosed diabetes increased by 70% between 1998/99 and 2008/09 (Public Health Agency of Canada, 2011), with a conservative total cost estimate of CAD$2.5 billion (excluding costs of complications) in 2000 and total direct healthcare costs projected to increase to over CAD$8 billion annually by 2016 (Ohinmaa et al., 2004). Similar trends have been observed for costs related to CVD, which accounted for over 30% of all deaths (17 million) worldwide in 2008 (World Health Organization, 2011). The global economic burden associated with the disease management costs of CVD was estimated to reach US$863 billion in 2010 and is projected to exceed 1 trillion by 2030 (World Health Organization, 2011). In Canada, 29% of all deaths in 2008 were secondary to CVD, which was estimated to cost upward of CAD$21 billion in annual healthcare expenditures (Conference Board of Canada, 2010).

Dietary behaviors consistent with guidelines for healthy eating have the potential to produce substantial health and economic benefits. Previous research has demonstrated that, for example, increased consumption of dairy, as well as reduced intakes of calories, sodium, and saturated fat would facilitate considerable health and economic benefits ranging from US$2 to $58 billion annually (McCarron and Heaney, 2004; Dall et al., 2009; Bibbins-Domingo et al., 2010). From a functional food perspective, Gyles et al. (2010) showed that direct and indirect coronary heart disease (CHD)-related costs could be reduced by CAD$38 million to $2.5 billion if Canadians increased intakes of phystosterols. More recently, Schmier et al. (2014, 2015) modeled the potential for substantial constipation-related savings in healthcare costs in the US and Europe from increased consumption of dietary fiber.

In Canada, the definition of dietary fiber includes carbohydrates that naturally occur in foods of plant origin and are not digested or absorbed by the small intestine of humans (Health Canada, 2012a). Among other disorders, dietary fiber has been associated with meaningfully lower prevalence of T2D and CVD (Merchant et al., 2003; Kendall et al., 2010; Chen et al., 2013). For instance, a meta-analysis of five cohorts (n = 239,485) showed a 19% lower risk of diabetes (RR = 0.81, 95% CI 0.70–0.93) among individuals in the highest quintile of dietary fiber intake (Anderson and Conley, 2007). Similarly, analysis of seven cohorts (n = 158,327) demonstrated that, compared to the lowest quintile of fiber intake, the highest levels of dietary fiber reduced risk of CHD by 29% (RR = 0.71, 95% CI 0.47–0.95; Anderson, 2004). Further systematic analysis of the available evidence has suggested that, compared to fruit or vegetable-derived fiber, diets with higher levels of fiber from cereals are associated with the greatest reduction in risk for T2D (Cho et al., 2013; InterAct Consortium, 2015) and CVD (Mozaffarian et al., 2003; Threapleton et al., 2013).

The average level of fiber consumed by Canadians is estimated to be 19.1 and 15.6 g per day for males and females, respectively (Belanger et al., 2014), and are well-below the IOM recommended adequate intakes for males (38 g per day) and females (25 g per day) between 19 and 50 years of age (Institute of Medicine, 2002). Sources of dietary fiber within the Canadian food supply are plentiful as both whole foods and fiber-fortified foods. Additionally, the Canadian population already has the necessary tools available in the marketplace to enact behavioral changes that would be consistent with increased intakes of dietary fiber. However, fiber education and motivation remain as long-term dietary challenges to consciously increase the consumption of fiber in Canada.

Given Canada's publically funded healthcare system, the promotion of dietary strategies that facilitate meaningful reductions in healthcare costs and prolong economic productivity can be considered a powerful tool for healthcare practitioners and policymakers attempting to manage economic resources. In this regard, the potential economic impact of increasing Canadians' fiber consumption can be calculated by determining the proportion of the economic burden related to T2D and CVD that can be avoided by increasing the consumption of dietary cereal fiber. Thus, the objective of this study was to evaluate the potential economic benefits of increased intakes of dietary cereal fiber for adults as determined by consequence reductions in annual healthcare costs associated with independently reduced rates of T2D and CVD in Canada.

Materials and Methods

Study Design

Utilizing data from the current medical literature and recent healthcare cost estimates from national databases, a three-step variation of a cost-of-illness analysis was conducted to evaluate the healthcare-related economic benefits of fiber consumption: (i) Determination of the *success rate*, which represents the proportion of the Canadian population expected to consume fiber-rich diets, (ii) Independent analysis of the *T2D and CVD reduction rate*s that would result from consumption of dietary fiber, and (iii) Estimation of the *healthcare cost savings* associated with reductions in T2D and CVD rates. Additionally, a sensitivity analysis of four scenarios (universal, optimistic, pessimistic, and very pessimistic) was created to cover a range of predictions within each of these steps.

Overall, three different sets of analyses were completed. The first analysis reflected the cost reductions in T2D and CVD-related healthcare services when cereal fiber is utilized to increase current actual intakes of dietary fiber for Canadian men (19.1 g per day) and women (15.6 g per day; Belanger et al., 2014) to the IOM's adequate intakes of 38 g per day and 25 g per day for men and women, respectively (Institute of Medicine, 2002). These are the cut-off values that policy makers, dietitians, and other healthcare providers in Canada and the US typically use

as guidelines. The second analysis examined the healthcare cost savings per g increase in cereal fiber intake. The third analysis estimated the total dollar savings at incremental levels of 20, 25, 30, and 35 g fiber per day for men and women alike, reflecting a moderate stepwise increase in cereal fiber consumption. **Table 1** summarizes the input parameters of the model. This analysis was applied to Canadian adults, which were defined as men and women ≥18 years of age. Demographic populace data was from 2014 and attained from Statistics Canada (Statistics Canada, 2015).

Step 1 of the Cost-of-Illness Analysis: *Assessing the Success Rate*

In economic theory, individuals make choices to maximize their utility, an unobservable metric for the satisfaction they receive from consuming goods or receiving services, subject to the constraints of time and financial resources. Previous research has explored how consumers maximize their utility in the context of food, nutrition, and health [Grossman (1972, March–April); Blaylock et al., 1999; Cawley, 2004]. More recent work (Lioutas, 2014) has examined the information processing behavior that consumers utilize as it relates to food choices. When an individual processes available dietary information and, based on this information, chooses to purchase and consume "healthy" foods, the individual is maximizing their utility. If this behavior is sustained over a period of time, the consumer may experience a health improvement.

The eventual economic benefit of increased dietary fiber intake is dependent on individual consumer decisions within the marketplace. Therefore, any model which attempts to measure the potential public health benefits should start with an examination of consumer behavior. A key assumption in health psychology and economics is that behavioral changes are the result of a decision-making process, where the benefits and costs of particular changes are considered before the adoption of a specific course of action. In previous short-term research that assessed consumer behavior in relation to dietary fiber intakes and health claims, fiber was found to be viewed favorably (Mialon et al., 2002; Dean et al., 2007; Baixauli et al., 2009; Ginon et al., 2009; Tudoran et al., 2009). For instance, when grain products were labeled as high in fiber and provided to consumers, enhanced likelihood of consumption (Mialon et al., 2002) as well as higher acceptability and purchase intentions (Baixauli et al., 2009) were reported. However, the actual long-term intake behavior for dietary fiber has not been previously measured. As such, in order to estimate the percent of the population expected to adopt a fiber-rich diet in Canada, a sensitivity analysis of universal, optimistic, pessimistic, and very pessimistic success rate scenarios was modeled based on findings from previous research (Mialon et al., 2002; Dean et al., 2007; Baixauli et al., 2009; Ginon et al., 2009; Tudoran et al., 2009). The universal fortification scenario assumed a 100% success rate and represented a dramatic shift in the dietary habits of Canadians. While this scenario is not realistically achievable in the short-term, it represents the maximum potential of economic savings with increased fiber intake over the very long-term. The optimistic success rate was assumed to be 50%, and represented a medium- to short-term pragmatic estimate of the potential economic savings possible through an increased dietary fiber intake. The pessimistic and very pessimistic success rates were set at 15% and 5% to respectively represent a less positive (but practical) short-to-medium term estimate of economic savings following increased fiber intake, and determine the impact on the cost estimates when assumptions are more pessimistic than normal.

TABLE 1 | Summary of the input parameters for the cost saving assessment model.

Parameter	Men	Women	Source
Current fiber intake, g per day	19.1	15.6	Belanger et al. (2014)
Target fiber intake, g per day			
	38	25	Institute of Medicine (2002)
	20	20	Assumption for the economic valuation of incremental increases in intake
	25	25	
	30	30	
	35	35	
	20.1	16.6	Assumption for economic valuation of a per g increase in intake
T2D reduction per 1 g cereal fiber intake, %	2.5	2.5	InterAct Consortium (2015)
CVD reduction per 1 g cereal fiber intake, %	1.1	1.1	Threapleton et al. (2013)

CVD, cardiovascular disease; IOM, Institute of Medicine; T2D, type 2 diabetes.

Step 2 of the Cost-of-Illness Analysis: *Estimating Disease Reduction due to Increased Dietary Cereal Fiber Intake*

Several epidemiological and dietary intervention studies of different designs have documented beneficial impacts of increased dietary fiber intake on disease risk and mortality rates. Similar to Step 1 of this analysis, we established possible scenarios regarding reductions in the incidence of T2D and CVD with higher intakes of dietary fiber based on the current English-language medical and nutritional literature. After careful examination of the available literature, model assumptions were generated based on two recent comprehensive systematic meta-analyses by Threapleton et al. (2013) and InterAct Consortium (2015). Eligibility criteria and quality of studies are included in the meta-analyses of choice. Under the context of this study and the studies reviewed, cereal fiber refers to fiber from cereal grains.

Estimated Effect of Increased Dietary Cereal Fiber on Prevalence of Type 2 Diabetes

The inverse relationship between increased dietary fiber and rates of T2D risk were estimated from a meta-analysis by InterAct Consortium (2015) based on data from prospective studies, where a per 10 g increase in cereal fiber resulted in an average of 25% reduced risk of T2D (RR = 0.75, 95% CI 0.65–0.86). These results are corroborated by a previous systematic review by Cho

et al. (2013), where cereal fiber consumption was estimated to decrease the risk of T2D by 18–40%.

Estimated Effect of Increased Dietary Cereal Fiber on Prevalence of Cardiovascular Disease

Similar to the T2D component, data for the estimated CVD risk reduction with higher intakes of dietary fiber was derived from a systematic review and meta-analysis of cohorts by Threapleton et al. (2013). There, based on a pooled estimate from prospective studies, consumption of cereal fiber intake was found to be inversely associated with risk of CVD (RR = 0.92 per 7 g per day, 95% CI 0.84–1.0), equivalent to a 1.1% lower CVD risk per g cereal fiber consumed.

Based on the meta-analytic data from Threapleton et al. (2013) and InterAct Consortium (2015), our analysis assumed that for each 1 g increase in dietary cereal fiber, incidence of T2D and CVD would be conservatively decreased by 2.5 and 1.1%, respectively (**Table 1**). For the purpose of this modeling exercise, it is assumed that the relative risk reduction of T2D and CVD per g cereal fiber intake corresponds to a decrease in the population-wide incidence of T2D and CVD of the same magnitude.

Step 3 of the Cost-of-Illness Analysis: *Estimating the Potential Annual Savings in Costs Associated with Type 2 Diabetes and Cardiovascular Disease*

Individual consumers are the primary beneficiary of any health improvement following increased consumption of dietary fiber. However, in a publicly funded healthcare system, such as the system adopted by Canada, more widespread benefits can also be expected. A reduction in T2D and CVD rates will result in the diversion of fewer resources to the treatment of these highly prevalent health conditions. Given a subsequent reduction in morbidity and mortality that are secondary to improved dietary habits of the population, society will also benefit from increased productivity. In this way, although consumers make deliberate dietary choices, such as increasing fiber intake, without considering the effect on healthcare expenses, the overall impact of their actions on society can be considerable.

The economic cost of disease in Canada is generally broken down into direct and indirect categories. Direct costs are those incurred by the healthcare system with the goal of improving and/or preventing a patient's health status from deteriorating. These usually include hospital care, drug, physician visits, and, sometimes, other "miscellaneous" costs. Indirect costs, on the other hand, are commonly known as those incurred by the loss of productivity to society arising from mortality and morbidity. A detailed description of the calculations used to determine the direct and indirect disease costs in Canada can be found in the *EBIC 2005–2008* Report (Public Health Agency of Canada, 2014).

Overview of Type 2 Diabetes Costs

The *EBIC 2005–2008* report (Public Health Agency of Canada, 2014) recently provided a comprehensive overview of the cost of diabetes in Canada. The Statistics Canada Consumer Price Index (health and personal care sub-index) was used to inflate the 2008 estimate of CAD$2.3 billion to 2014 levels and yielded CAD$2.5 billion as the best estimated total direct and indirect economic costs of T2D (**Table 2**).

Estimated at CAD$1.3 billion in 2014 dollars, drugs constituted the largest direct costs of T2D, which includes the costs of prescribed and non-prescribed medications purchased in retail stores. Since many different medications are used to treat T2D, it is reasonable that a decrease in the overall incidence of the disease would subsequently lead to a decrease in T2D drug-related costs. Hospitalization costs of T2D, estimated at CAD$527.2 million in 2014 dollars, were calculated on the basis of bed occupation and aggregated by diagnostic category. Generally, hospital costs are largely the fixed costs related to operating and maintaining hospital facilities, as well as the salaries of the medical professionals and support staff. The more variable components of hospitalization include the cost of medications administered to the hospitalized patients, the cost of food and accommodation, and the cost of diagnostic procedures carried out in hospitals. A reduction in the incidence of T2D would be anticipated to lead to fewer hospitalizations resulting from this disorder and, as a consequence, reductions in variable costs. Finally, the physician costs were calculated based on fee-for-service billings submitted to provincial health insurance plans and are allocated on the basis of the primary diagnostic category. For example, if a patient visits a physician's office for a follow-up treatment after a first diagnosis of T2D, this cost would be attributed to the cost of T2D. The estimated cost of T2D-related visits to physicians was approximately CAD$521.4 million in 2014 dollars. It follows that a reduction in overall T2D levels will result in fewer doctor visits, which will reduce these costs. Total indirect costs for T2D were estimated at CAD$155.4 million in 2014 dollars, including $13.2 million for mortality and $142.2 million for morbidity. In estimating the mortality costs of T2D, *EBIC 2005–2008* report utilized the friction cost approach, which assumes that sick and deceased workers can be replaced after a certain period

TABLE 2 | Estimated direct and indirect costs of type 2 diabetes in Canada (CAD $).

Cost category	2008* ($millions)	2014† ($millions)
Direct costs		
Hospital	492.7	527.2
Physician	487.3	521.4
Drugs	1,198.2	1,282.1
Total direct costs	**2,178.2**	**2,330.7**
Indirect costs		
Mortality	12.3	13.2
Morbidity	132.9	142.2
Total indirect costs	**145.2**	**155.4**
Total costs	**2,323.4**	**2,486.0**

**From the EBIC 2005–2008 report (Public Health Agency of Canada, 2014).*
†Current dollars based on adjustments of inflation rates according to Statistics Canada Consumer Price Index.

of time known as the 'friction period.' Cost estimates of this method are normally lower than those derived from the classical human capital method. A reduction in the incidence of T2D is assumed to lead to decreases in both components of the indirect costs.

Analysis of Type 2 Diabetes Cost Reduction

The reduction in the cost of T2D was assumed to be linear when a decline in T2D incidence is observed. The exception was for the variable costs related to hospitalization. As described earlier, fixed and variable costs exist in hospitalization. The former is incurred regardless of the prevalence of any disease, whereas the latter is largely affected by the number of admissions. A comprehensive breakdown of hospital care costs in Canada is, to our knowledge, not available. As a result, it was necessary to approximate the portion of hospital costs that are fixed and not affected from reduced incidence of T2D. Previous research has provided a breakdown of fixed and variable costs in American hospitals and found that hospital costs are approximately 84% fixed and 16% variable (Roberts et al., 1999). Thus, for the purpose of this research, it was assumed that a reduction in T2D would not result in reductions in fixed costs of hospitalization, but would facilitate a proportional reduction in the variable costs. This means that each 1% reduction in the incidence of T2D would be followed by a 0.16% reduction in hospital costs.

It is reasonable to assume that fewer individuals with T2D will require less medication for treatment. As such, a proportional reduction was assumed for drug costs. Similarly, given that the physician care costs are based on physician billings, which are in turn based on T2D patient visits to doctors' offices, a reduction in T2D was assumed to lead to a proportional reduction in T2D-related physician costs. Finally, as the number of cases with T2D decreases, costs associated with mortality and morbidity were assumed to follow in a proportional manner. A summary of the relationship between T2D incidence and associated costs is provided in **Table 3**.

Overview of Cardiovascular Disease Costs

The *EBIC 2005–2008* (Public Health Agency of Canada, 2014) and the *NHEX 1975–2013* (Canadian Institute for Health Information, 2013) expense figures were both used as the foundation of the estimates of CVD in this analysis; again with adjustments to 2014 dollars using the Statistics Canada Consumer Price Index (health and personal care sub-index). Inflating values from the most recent 2008 estimate of CAD$12.2 billion to 2014 dollars yielded a revised valuation of CAD$13.0 billion as the best estimated economic cost of CVD in Canada. In the case of CVD, the direct costs as presented by the *EBIC 2005–2008* report include hospital care, drug, and physician visits, whereas the indirect costs include mortality and morbidity. These costs are explained further in the subsections below and summarized in **Table 4**.

The largest direct costs associated with CVD were the hospitalization costs, which were estimated at slightly more than CAD$5.4 billion in 2014 dollars. Again, the fixed costs associate with operating hospital facilities and the staff salaries, while the variable costs associate with drugs administered to the hospitalized patients, food, and diagnostic procedures. Similar to T2D estimates, only the variable costs are expected to decrease with fewer hospitalizations resulting from reductions in the incidence of CVD. Prescribed drug costs of CVD were estimated at CAD$4.6 billion in 2014 dollars and, similar to the T2D estimates, are logically expected to decrease with better management of the disease. The physician care costs were CAD$2.5 billion in 2014 dollars and, similar to the drug costs, are expected to decrease with fewer physician visits when CVD rates decrease. Finally, the "other direct costs" associated with CVD were estimated at CAD$143.5 million in 2014 dollars and are based on estimates of services of other health professionals (e.g., physiotherapists), public health, administration, and ambulance services from the *NHEX 1975–2013* report (Canadian Institute for Health Information, 2013). A reduction in CVD will reduce

TABLE 3 | Summary of direct and indirect cost reductions that correspond to a 1% decrease in the incidence of type 2 diabetes.

Cost category	% Reduction
Direct costs	
Hospital*	0.16%
Drugs	1.00%
Physician care	1.00%
Indirect costs	
Mortality	1.00%
Morbidity	1.00%

**Based on the estimation that 16% of hospitalization costs are variable (i.e., medications and supplies) and 84% are fixed (i.e., salaries, buildings, and equipments; Roberts et al., 1999).*

TABLE 4 | Estimated direct and indirect costs of cardiovascular disease in Canada (CAD $).

Cost category	2008* ($millions)	2014† ($millions)
Direct costs		
Hospital	5,068.0	5,422.8
Drugs	4,272.7	4,571.8
Physician care	2,352.0	2,516.6
Other direct‡	134.1	143.5
Total direct costs	**11,826.8**	**12,654.7**
Indirect costs		
Mortality	92.4	98.9
Morbidity	269.6	288.5
Total indirect costs	**362.0**	**387.3**
Total costs	**12,188.8**	**13,042.0**

**From the EBIC 2005–2008 report (Public Health Agency of Canada, 2014). †Current dollars based on adjustments of inflation rates according to Statistics Canada Consumer Price Index. ‡Represents cost estimates for Other Professionals (chiropractors, physiotherapists, private duty nurses, etc.) and Other Health Spending (home care, medical transportation, etc.) by the National Health Expenditure Trends 1975–2013 report (Canadian Institute for Health Information, 2013) where total Other Direct costs for all diseases in 2008 reached CAD$53.0 billion. Percentage of CVD relative to total Other Direct costs within the EBIC 1998 report (Public Health Agency of Canada, 1998) of 0.3% was used to estimate the 2008's CVD-related other direct economic valuation of CAD$134.1 million and then adjust it to a 2014 estimate of CAD$143.5 million.*

the demand for some, but not all, of the above-mentioned services and, as a result, reduces a portion of this component of direct costs.

In estimating the CVD-related mortality costs of CAD$98.9 million in 2014 dollars, similar to the analysis for T2D by *EBIC 2005–2008*, these costs were derived using the friction cost approach. It is logical that a reduction in the incidence of CVD and the corresponding decrease in mortality will reduce this cost. Morbidity, or disability, costs arise when productivity is lost due to illness for a period of time. The estimated economic burden of morbidity resulting from CVD in the *EBIC 2005–2008* report was CAD$288.5 million in 2014 dollars. Akin to the mortality component, morbidly costs are expected to decrease with a reduction in the incidence of CVD.

Analysis of Cardiovascular Disease Cost Reduction

Similar to the T2D cost reduction, with lower CVD rates, our CVD cost reduction analysis assumed a proportional reduction in the variable (but not the fixed) hospitalization costs, drug costs, and physician costs (**Table 5**). Unlike the previous report in Public Health Agency of Canada (1998), the new *EBIC 2005–2008* report does not provide cost estimates for services by "other health providers" for CVD, which necessitated estimations using figures from the *NHEX 1973–2013* and *EBIC 1998* reports as previously described. The costs for "Other" (5.4%), within the "Other Professionals" category (Canadian Institute for Health Information, 2013), which includes chiropractors, physiotherapists, private duty nurses, and others, were expected to be reduced in a manner proportional to the overall CVD reduction. Similarly, costs that will likely be reduced by a reduction in CVD include home care, medical transportation, training of health workers, and others (13.8%) within the *NHEX* "Other Health Spending" category. The final result was that a 1% decrease in the incidence of CVD will result in a 0.19% reduction in other direct CVD-related costs.

TABLE 5 | Summary of direct and indirect cost reductions that correspond to a 1% decrease in the incidence of cardiovascular disease.

Cost category	% Reduction
Direct costs	
Hospital*	0.16%
Drugs	1.00%
Physician care	1.00%
Other direct†	0.19%
Indirect costs	
Mortality	1.00%
Morbidity	1.00%

**Based on the estimation that 16% of hospitalization costs are variable (i.e., medications and supplies) and 84% are fixed (i.e., salaries, buildings, and equipments; Roberts et al., 1999). †Based on total disease cost by the EBIC 2005–2008 report (Public Health Agency of Canada, 2014) and estimates from the National Health Expenditure Trends 1975–2013 report (Canadian Institute for Health Information, 2013) for Other Professionals (5.4%) and Other Healthcare Spending (13.8%) categories.*

Finally, also similar to the T2D case, morbidity and mortality costs were assumed to have a directly proportional CVD-reduction to cost-reduction relationship. Basically, since the incidence of CVD will decrease, it is a reasonable assumption that a proportional reduction in the deaths and disability from CVD will be observed. As a consequence, the loss of human capital that would ordinarily be incurred from CVD-related death and disability does occur and this facilitates an economic benefit.

Results

Tables 6 and **7** summarize the potential T2D and CVD direct and indirect cost savings when current levels of fiber intake (19.1 g per day for men and 15.6 g per day for women; Belanger et al., 2014) are increased with cereal fiber to levels that correspond to the IOM's recommended adequate intakes. Under the universal fortification scenario, assuming a 100% success rate and maximum potential of economic savings over the very long run, our analysis predicted total annual healthcare and related savings of CAD$718.8 million for T2D and $1.3 billion for CVD costs. The optimistic scenario, which assumed a 50% success rate and medium- to short-term savings, on the other hand, predicted savings of CAD$359.4 million for T2D and $647.8 million for CVD costs annually. With a 15% success rate and a less positive, yet still practical, short- to

TABLE 6 | Potential savings in type 2 diabetes costs among Canadian adults from improved intake of dietary cereal fiber (CAD $million).

	Scenario			
Cost category	**Universal**	**Optimistic**	**Pessimistic**	**Very pessimistic**
Direct cost savings				
Hospital	29.7	14.8	4.5	1.5
Physician	183.4	91.7	27.5	9.2
Drugs	451.0	225.5	67.7	22.6
Total direct cost savings	**664.1**	**332.1**	**99.6**	**33.2**
Indirect cost savings				
Mortality	4.6	2.3	0.7	0.2
Morbidity	50.0	25.0	7.5	2.5
Total indirect cost savings	**54.7**	**27.3**	**8.2**	**2.7**
Total cost savings	**718.8**	**359.4**	**107.8**	**35.9**

*Data represent T2D-related economic savings from the utilization of cereal fiber for increasing dietary fiber consumption from current levels (**Table 1**) to levels that correspond to the IOM's adequate intake cut-offs, estimated at 38 g per day for men and 25 g per day for women (Institute of Medicine, 2002). The universal fortification represents the best-case scenario of potential cost savings if all Canadian adults (≥18 years of age) were to consume the adequate quantities of dietary fiber. The optimistic scenario is a medium- to short-term pragmatic estimate of the potential cost savings when 50% of adults increase intakes of dietary fiber. The pessimistic scenario is a practical short- to medium-term estimate of cost savings that could follow the increase in dietary cereal fiber intakes among 15% of adults. The very pessimistic scenario represents the worst-case estimate when up to 5% of adults make the dietary change.*

TABLE 7 | Potential savings in cardiovascular disease costs among Canadian adults from improved intake of dietary cereal fiber (CAD $million).

	Scenario			
Cost Category	**Universal**	**Optimistic**	**Pessimistic**	**Very pessimistic**
Direct cost savings				
Hospital	134.3	67.2	20.1	6.7
Drugs	707.7	353.8	106.1	35.4
Physician care	389.5	194.8	58.4	19.5
Other direct	4.2	2.1	0.6	0.2
Total direct cost savings	**1,235.7**	**617.9**	**185.4**	**61.8**
Indirect cost savings				
Mortality	15.3	7.7	2.3	0.8
Morbidity	44.7	22.3	6.7	2.2
Total indirect cost savings	**60.0**	**30.0**	**9.0**	**3.0**
Total cost savings	**1,295.7**	**647.8**	**194.4**	**64.8**

*Data represent CVD-related healthcare savings from the utilization of cereal fiber for increasing dietary fiber consumption from current levels (**Table 1**) to levels that correspond to the IOM's adequate intake cut-offs, estimated at 38 g per day for men and 25 g per day for women (Institute of Medicine, 2002). The universal fortification represents the best-case scenario of potential cost savings if all Canadian adults (≥18 years of age) were to consume the adequate quantities of dietary fiber. The optimistic scenario is a medium- to short-term pragmatic estimate of the potential cost savings when 50% of adults increase intakes of dietary fiber. The pessimistic scenario is a practical short- to medium-term estimate of cost savings that could follow the increase in dietary cereal fiber intakes among 15% of adults. The very pessimistic scenario represents the worst-case estimate when up to 5% of adults make the dietary change.*

medium-term effects, the pessimistic scenario showed savings of CAD$107.8 million for T2D and $194.4 million for CVD costs. Finally, the very pessimistic scenario that assumed a worst-case estimate of a 5% success rate suggested total annual savings of CAD$35.9 million for T2D and $64.8 million for CVD costs.

Potential T2D and CVD cost savings with each 1 g per day increase in dietary cereal fiber intake are presented in **Tables 8** and **9**, respectively. There, given predicted worst-to-best case scenarios, total annual cost savings ranged between CAD$2.6 and $51.1 million for T2D, and $4.6 and $92.1 million for CVD.

Summarized in **Tables 10** and **11** are the predicted economic savings when cereal fiber was used to incrementally increase Canadian adult's current dietary fiber intakes to 20, 25, 30, and 35 g per day for men and women alike. For T2D, the very pessimistic, pessimistic, optimistic, and universal scenarios' total savings ranged from CAD$6.8 to $45.2 million, $20.5 to $135.5 million, $68.4 to $451.5 million, and $136.8 to $903.0 million, respectively (**Table 10**). Likewise, savings in CVD healthcare and related costs were estimated to range between CAD$12.3 and $81.4 million (very pessimistic), $37.0 and $244.2 million (pessimistic), $123.3 and $813.9 million (optimistic), and $246.7 million and $1.6 billion (universal) with increasing the current fiber intakes of Canadian adults to 20, 25, 30, and 35 g per day, respectively (**Table 11**).

TABLE 8 | Potential savings in type 2 diabetes cost among Canadian adults for each 1 g per day increase in intakes of dietary cereal fiber (CAD $million).

	Scenario			
Cost category	**Universal**	**Optimistic**	**Pessimistic**	**Very pessimistic**
Direct cost savings				
Hospital	2.1	1.1	0.3	0.1
Physician	13.0	6.5	2.0	0.7
Drugs	32.1	16.0	4.8	1.6
Total direct cost savings	**47.2**	**23.6**	**7.1**	**2.4**
Indirect cost savings				
Mortality	0.3	0.2	0.1	0.0
Morbidity	3.6	1.8	0.5	0.2
Total indirect cost savings	**3.9**	**1.9**	**0.6**	**0.2**
Total cost savings	**51.1**	**25.5**	**7.7**	**2.6**

The universal fortification represents the best-case scenario of potential cost savings in all Canadian adults (≥18 years of age). The optimistic scenario is a medium- to short-term pragmatic estimate of the potential cost savings in 50% of adults. The pessimistic scenario is a practical short- to medium-term estimate of cost savings that could follow the 1 g per day increase in dietary cereal fiber intakes among 15% of adults. The very pessimistic scenario represents the worst-case estimate when up to 5% of adults increase their dietary cereal fiber intakes by 1 g per day.

Discussion

Using a cost-of-illness analysis, this study assessed the potential savings in costs of T2D and CVD within the Canadian healthcare system following higher intakes of dietary cereal fiber among adults. The potential economic benefits that resulted from improved intake of cereal fiber were significant. Specifically, if between 5 and 100% of the Canadian adults were to utilize cereal fiber to adopt intakes of dietary fiber that correspond to the IOM's adequate intake levels (Institute of Medicine, 2002), approximately CAD$36 to $720 million and CAD$65 million to $1.3 billion would accrue as total annual savings in healthcare and related costs associated with T2D and CVD, respectively. These savings are substantial relative to the current healthcare budget in Canada.

The rising costs of healthcare are a growing concern, especially in Canada where direct costs of treating disease are borne largely by an increasingly aging public. Any opportunity to reduce these costs should be fully studied. The health benefits of increased dietary fiber intakes are well-recognized. Accumulating evidence suggests protection against a range of major public health concerns, including diabetes (Murtaugh et al., 2003; Schulze et al., 2007), CVD (Liu et al., 1999; Pereira et al., 2004), obesity (Liu et al., 2003), cancers (Aune et al., 2011, 2012), and gastrointestinal disorders (Petruzziello et al., 2006), all of which place substantial burdens on healthcare resources in Canada and, likewise, around the globe. Still, very little knowledge is available on the economic benefits of greater habitual or recommended intakes of fiber. We are unaware of other economic analyses that have previously

TABLE 9 | Potential cardiovascular disease cost savings among Canadian adults for each 1 g per day increase in intakes of dietary cereal fiber (CAD $million).

Cost category	Scenario			
	Universal	Optimistic	Pessimistic	Very pessimistic
Direct cost savings				
Hospital	9.5	4.8	1.4	0.5
Drugs	50.3	25.1	7.5	2.5
Physician care	27.7	13.8	4.2	1.4
Other direct	0.3	0.1	0.0	0.0
Total direct cost savings	**87.8**	**43.9**	**13.2**	**4.4**
Indirect cost savings				
Mortality	1.1	0.5	0.2	0.1
Morbidity	3.2	1.6	0.5	0.2
Total indirect cost savings	**4.3**	**2.1**	**0.6**	**0.2**
Total cost savings	**92.1**	**46.0**	**13.8**	**4.6**

The universal fortification represents the best-case scenario of potential cost savings in all Canadian adults (≥18 years of age). The optimistic scenario is a medium- to short-term pragmatic estimate of the potential cost savings in 50% of adults. The pessimistic scenario is a practical short- to medium-term estimate of cost savings that could follow the 1 g per day increase in cereal dietary fiber intakes among 15% of adults. The very pessimistic scenario represents the worst-case estimate when up to 5% of adults increase their dietary cereal fiber intakes by 1 g per day.

TABLE 10 | Summary of potential total savings in type 2 diabetes costs among Canadian adults with incremental increases in intakes of dietary cereal fiber (CAD $million).

	20 g per day	25 g per day	30 g per day	35 g per day
Universal	136.8	392.2	647.6	903.0
Optimistic	68.4	196.1	323.8	451.5
Pessimistic	20.5	58.8	97.1	135.5
Very pessimistic	6.8	19.6	32.4	45.2

*Based on differences from current intakes of dietary fiber (**Table 1**), the universal fortification represents the best-case scenario of potential cost savings if all Canadian adults (≥18 years of age) were to use cereal fiber to increase daily fiber intakes to 20, 25, 30, or 35 g per day for men and women. The optimistic scenario is a medium- to short-term pragmatic estimate of the potential cost savings when 50% of adults adopt the incremental increases in intakes of dietary fiber. The pessimistic scenario is a practical short- to medium-term estimate of cost savings that could follow the incremental increases in dietary fiber intakes among 15% of adults. The very pessimistic scenario represents the worst-case estimate when up to 5% of adults make the dietary changes.*

assessed the potential savings in T2D- and CVD-related costs when dietary fiber consumption is increased. Although, a few recent studies have reported the valuable effects of increased fiber intakes on healthcare costs for functional constipation in the US (Schmier et al., 2014) and Europe (Schmier et al., 2015).

Clinical and epidemiological research continues to delineate the benefits of foods and nutrients with respect to general health as well as reduced risk of chronic disease. Such data are useful for developing and adjusting dietary recommendations.

TABLE 11 | Summary of potential total savings in cardiovascular disease costs among Canadian adults with incremental increases in intakes of dietary cereal fiber (CAD $million).

	20 g per day	25 g per day	30 g per day	35 g per day
Universal	246.7	707.0	1,167.4	1,627.8
Optimistic	123.3	353.5	583.7	813.9
Pessimistic	37.0	106.1	175.1	244.2
Very pessimistic	12.3	35.4	58.4	81.4

*Based on differences from current intakes of dietary fiber (**Table 1**), the universal fortification represents the best-case scenario of potential cost savings if all Canadian adults (≥18 years of age) were to use cereal fiber to increase daily fiber intakes to 20, 25, 30, or 35 g per day for men and women. The optimistic scenario is a medium- to short-term pragmatic estimate of the potential cost savings when 50% of adults adopt the incremental increases in intakes of dietary fiber. The pessimistic scenario is a practical short- to medium-term estimate of cost savings that could follow the incremental increases in dietary fiber intakes among 15% of adults. The very pessimistic scenario represents the worst-case estimate when up to 5% of adults make the dietary changes.*

Given that the definition of dietary fiber is broad in scope and can include indigestible carbohydrate from a variety of dietary sources (Health Canada, 2012a), it is reasonable that different fibers from diverse foods impose unique health benefits. Based on supportive data from published risk analyses, this economic valuation focused on cereal fiber as a means of reducing future incidence of T2D and CVD. It is important to note, however, that this analysis does not support a reductionist approach to healthful diets; where cereal fiber is identified as the only fiber that can facilitate health and economic benefits. For example, while cereal fibers are efficacious for decreased T2D and CVD risk, other fibers, and the foods containing them, such as fruits and vegetables, are widely accepted as part of healthy diet. Accordingly, this analysis modeled the addition of cereal fiber to current fiber intakes (19.1 g for men and 15.6 g for women), which recognizes a baseline dietary fiber consumption from various dietary sources. This study does support, however, that health as well as economic benefits could arise if Canadians impose more healthful lifestyles. From this and other nutritional economic data (McCarron and Heaney, 2004; Dall et al., 2009; Bibbins-Domingo et al., 2010; Gyles et al., 2010; Schmier et al., 2014, 2015), it is logical that as healthy lifestyle habits compound, societal benefits will also grow in parallel.

For T2D and CVD, results from this study complement those from Schmier et al. (2014, 2015) and highlight the importance of communicating such health benefits of dietary fiber to the general public and various stakeholders. For the food industry, emphasis on the provision of higher-fiber foods could help facilitate a national economic benefit. Government and healthcare professionals are crucial for implementing strategies that capitalize on potential success of realizing any economic savings from increasing fiber consumption in Canada. Policy makers will need to set clear guidelines that facilitate a high degree of utility for consumers by setting guardrails around the type(s) of health claims permitted that ensure consistent and credible message is received by consumers. Finally, educators and healthcare providers will play a crucial role in

emphasizing the importance of dietary fiber to patients and the public.

While this cost-of-illness analysis demonstrated the potential for substantial healthcare savings with increased consumption of cereal fiber, it is reasonable that there would be costs associated with the implementation of initiatives that impose such dietary changes for Canadians. These costs would majorly be incurred by two of the aforementioned stakeholders: government(s) and the consumer. Government spending would manifest as programs that promote the consumption foods that impact the Canadian healthcare economic landscape, such as dietary sources of cereal fiber. Initiatives could include increased emphasis for cereal-derived fiber within current programs such as Canada's Food Guide (Health Canada, 2011) as well as independent marketing campaigns. As a partnership with the food industry, the latter strategy has been utilized to increase Canadians' awareness and use of the Nutrient Facts Table on Canadian food labels (Government of Canada, 2015). While new and refreshed programs would be of value for heightening dietary awareness of foods that could impact healthcare costs, governments and regulatory agencies across jurisdictions, including Canada, have already implemented a regulatory framework that promote the consumption of specific cereal fibers that are directly linked with reduced risk factors for CVD. For example, Health Canada, The Food and Drug Administration, The European Commission, and Food Standards Australia New Zealand permit front-of-pack health claims on foods that communicate the presence of defined threshold levels of oat or barley-derived beta-glucan and their ability to lower circulating cholesterol levels (Health Canada, 2010, 2012b; European Commission, 2011, 2012; Food and Drug Administration, 2013; Zealand FSAN, 2014). Perhaps, further funding allocation is required to bring increased awareness to specific health claims in market, as well as increased use of sources of cereal fiber by industry.

For the second stakeholder, the consumer, the most significant costs incurred would be those required for imposing dietary change. While this analysis provided cost savings per g increase in cereal fiber consumption, it is ideal if increased consumption of cereal fiber among Canadians surpassed one g per day. That being said, within Canada and other regions, foods with cereal fiber are ubiquitous within the food supply as foods with whole grain and/or added bran. Moreover, dietary recommendations across jurisdictions promote the consumption of whole grains, which are sources of cereal fiber (United States Department of Agriculture, 2010; Health Canada, 2011; Australian Government, 2013). Whole grains are also primary components of healthful traditional diets such as the Mediterranean and Nordic Diet (Jensen and Poulsen, 2013; Gerber and Hoffman, 2015). For some consumers, there could be a cost to consuming a healthier diet that incorporates efficacious increases in specific nutrients such as dietary cereal fiber (Jensen and Poulsen, 2013). However, when the biological need to consume food is combined with minimal consumption of foods or constituents that counteract the health benefits of cereal fiber, these costs to the consumer would be marginal; and align with the costs realized if the populace fully embraced regional dietary guidance from governments, dietitians, and other healthcare practitioners.

In addition to government and consumers, industry is also a critical stakeholder for facilitating dietary changes among Canadians, including increased consumption of cereal fiber. Given that it is the food industry that manufactures and supplies a significant proportion of the foods that comprise the diets of Canadians, it is reasonable that increased demand for sources of dietary cereal fiber would also incur an upfront cost to industry. These costs would come from new product innovation, renovation of existing products, manufacturing, shipping, listing fees, and marketing. While upfront costs to the food industry are realized, strong demand for nutritious food with cereal fiber will drive continued support for the development of foods that contain whole grains and/or added bran. Governments already impose regulations that outline thresholds regarding the minimum levels of dietary fiber required to make "source of fiber" claims of varying magnitude (European Commission, 2006; Zealand FSAN, 2014; The Canadian Food Inspection Agency, 2015). Meeting these threshold levels is crucial for permitting industry to communicate healthful food attributes to the Consumer. In addition to artisan or unprocessed foods that contain fiber from cereal grains, epidemiological studies that demonstrate an inverse association between cereal fiber and risk of diabetes, CVD, and mortality include foods manufactured by the food industry, such as fiber-containing ready-to-eat cereals (Cho et al., 2013; Huang et al., 2015). Continued emphasis from nutrition leaders in the private and public sectors as well as food innovation that facilitates widespread consumption of foods with efficacious levels of cereal fiber will be critical for widespread healthcare cost savings from dietary change.

As discussed previously, to our knowledge, this work is the first to examine the potential savings in costs to the Canadian healthcare system attributed to higher intakes of dietary fiber manifesting in lower rates of T2D and CVD. We utilized the most recent literature and national databases for findings pertaining to identification of the consumer trends and healthcare costs. Developing three sets of analyses enabled the prediction of healthcare cost savings that are mostly communicable to policy makers, dietitians, and other healthcare providers. For example, while IOM target levels of fiber intakes are likely most beneficial for government policy makers and healthcare associations that set guidelines for clinical practice, incremental targets are mainly beneficial to the general public and healthcare practitioners who focus on a stepwise approach for assisting patients with increasing fiber consumption.

This study also has limitations. Estimates of risk reduction per g cereal fiber were derived from studies that gave prescribed levels of cereal fiber. Thus, it was assumed that the relationship between cereal fiber dose and risk reduction was linear. However, in some cases a linear dose effect may not exist across all levels of cereal fiber consumed; and, in those instances, thresholds for cereal fiber intake must be met for increased risk reduction. Recently, data from the InterAct Consortium demonstrated that an inverse effect of cereal fiber on T2D risk was linear with a steeper slope at >10 g/day (InterAct Consortium, 2015). That being said, the cost-of-illness analysis in this study utilized

conservative estimates of risk reduction that were generated from meta-analyses and were assumed to be constant across all dosages of cereal fiber. Moreover, fiber-containing foods that are recommended by healthcare practitioners and dietary guidelines typically contain substantial levels of dietary fiber that would assist consumers in consuming >1 g cereal fiber per serving and per day.

Another limitation of the present work may relate to the fact that isolating the reported health benefits of dietary cereal fiber intakes from other associated lifestyle and environmental factors is difficult. Fiber intake from certain sources, such as fruits and vegetables, usually associates with better socio-economic status (Dubowitz et al., 2008; Boylan et al., 2011), such as higher education and income, thus possibly healthier overall environments. To what extent these other lifestyle factors that associate with higher fiber intakes serve as confounders in our model remains to be assessed.

Conclusion

Given the economic burden of T2D and CVD in Canada and worldwide, the novel findings of this analysis shed light on the economic valuation of optimal dietary fiber intakes and reach beyond the well-established direct health benefits. Strategies to increase the consumers' general knowledge of the recommended intakes of dietary fiber, and benefits of cereal fiber, as part of healthy diet and overall lifestyle, and to facilitate stakeholder synergy, are highly warranted. Ultimately, such evidence-based strategies are expected to enable better management of healthcare and related costs associated with T2D and CVD.

Author Contributions

MA and CG designed the economic model, reviewed the literature, and carried out the monetary analyses. MA interpreted the data and drafted the manuscript with assistance from CM. CM, JC, and PJ conceived the study question. All authors contributed to the interpretation of data, critically reviewed the manuscript for important intellectual content, and approved the final version.

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MINI REVIEW
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The scale of the evidence base on the health effects of conventional yogurt consumption: findings of a scoping review

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Background: The health effects of conventional yogurt have been investigated for over a century; however, few systematic reviews have been conducted to assess the extent of the health benefits of yogurt.

Objective: The aim of this scoping review was to assess the volume of available evidence on the health effects of conventional yogurt.

Methods: The review was guided by a protocol agreed *a priori* and informed by an extensive literature search conducted in November 2013. Randomized controlled trials were selected and categorized according to the eligibility criteria established in the protocol.

Results: 213 studies were identified as relevant to the scoping question. The number of eligible studies identified for each outcome were: bone health (14 studies), weight management and nutrition related health outcomes (81 studies), metabolic health (6 studies); cardiovascular health (57 studies); gastrointestinal health (24 studies); cancer (39 studies); diabetes (13 studies), Parkinson's disease risk (3 studies), all-cause mortality (3 studies), skin complaints (3 studies), respiratory complaints (3 studies), joint pain/function (2 studies); the remaining 8 studies reported a variety of other outcomes. For studies of a similar design and which assessed the same outcomes in similar population groups, we report the potential for the combining of data across studies in systematic reviews.

Conclusions: This scoping review has revealed the extensive evidence base for many outcomes which could be the focus of systematic reviews exploring the health effects of conventional yogurt consumption.

Keywords: yogurt, health outcomes, review, effects, evidence

INTRODUCTION

Yogurt consumption has been associated with health and well-being for hundreds of years, but scientific research efforts on the potential health effects of conventional yogurt mainly started during the last century. Conventional yogurt contains a large quantity of nutrients essential for health and has relatively low calorie content, making it a high nutritional density product. In addition, the changes in milk constituents that occur during lactic acid fermentation influence the nutritional and physiological value of yogurt (Hewitt and Bancroft, 1985; Bianchi-Salvadori, 1986; Bourlioux and Pochart, 1988; Adolfsson et al., 2004). The efficacy of yogurt has been investigated in relation to a wide range of separate and overlapping outcomes including weight management (Burns et al., 1998), type 2 diabetes (O'Connor et al., 2014), cardiovascular disease risk (Buyuktuncer et al., 2013), bone health (Heaney et al., 2002), dental health (Telgi et al., 2013), the risk of various forms of cancer (Kurahashi et al., 2008), gastrointestinal (GI) health (Pashapour and Iou, 2006; Ballesta et al., 2008), lactose intolerance (Adibi et al., 2009), malnutrition (Sazawal et al., 2013), immunological parameters (Olivares et al., 2006), and overall mortality (Goldbohm et al., 2011). While a range of research designs have been employed to examine the health effects of yogurt, including observational studies (Cramer et al., 1989; Arslantas et al., 2008; Dawczynski and Jahreis, 2009) and experimental studies (Bonjour et al., 2013; Douglas et al., 2013), systematic reviews (and meta-analyses when appropriate) have been conducted in relation to only a few health outcomes (Tong et al., 2011; Aune et al., 2012, 2013; Soedamah-Muthu et al., 2012; Gao et al., 2013; O'Sullivan et al., 2013).

The objective of this scoping review was to assess the volume of evidence for the health effects of yogurt consumption. The scoping review focused on conventional yogurt as defined by the Codex Alimentarius. The Codex Alimentarius Commission was established in the 1960s by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) and represents an international reference point for food safety and consumer protection (WHO, 2006). The standard for fermented milks (CODEX STAN 243-2003) (Codex Committee on Milk and Milk Products, 2010) defines yogurt as specifically characterized by the presence of the symbiotic starter cultures *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus* (Codex Committee on Milk and Milk Products, 2010). Furthermore, it states that yogurt obtained through fermentation of milk by cultures of *Streptococcus thermophilus* and any other *Lactobacillus species* should be named through the use of an appropriate qualifier in conjunction with the word yogurt. This has commonly lead to the designation "probiotic yogurt" for fermented milk products containing a different micro-organism with a proven health benefit when taken in adequate amounts (WHO, 2001), and based on the rather widespread opinion that the conventional yogurt starter cultures should not be considered as probiotics.

This scoping review does not concern the tremendous amount of research findings on specific probiotic strains that has been generated during the past 20 years but concentrates on identifying the available evidence base on the generic health effects of conventional yogurt; an analysis undertaken as the first stage to inform potential future systematic reviews.

Abbreviations: GI, gastrointestinal; RCT, randomized controlled trial.

METHODS

This scoping review was conducted using relevant methods of the systematic review process up to the point of data extraction. It is reported in accordance with the PRISMA reporting guidelines statement and checklist (Liberati et al., 2009) up to that point. The scoping review does not include the detailed data extraction, quality assessment and synthesis of a full systematic review, but is conducted with the aim of being objective, extensive and transparent. The scoping review was guided by a protocol (available for download from www.yhec.co.uk), which was agreed before the searches were conducted.

Studies considered eligible for the scoping review were epidemiological studies, cohort studies, open label studies and randomized controlled trials (RCTs). Case reports, letters, comments, and editorials were not eligible for inclusion. Eligible studies had to fulfill the requirement of examining the effect of oral consumption of conventional yogurt in the general population, in relation to a range of health outcomes, with a few specific exclusions. Studies that only examined the health effects of yogurt in the following situations were excluded: human populations with specific diseases; any animal population; *in vitro* studies and studies using technologies that simulate the stomach environment. We also excluded studies if they only assessed the yogurt interventions in relation to any of the following: fecal count outcomes; outcomes relating to stomach flora; overall assessments of diets where yogurt is only one factor and not reported separately; dental health, lactose intolerance; contagious diseases; treatment of infectious GI/respiratory tract diseases; studies reporting laboratory or immunological parameters only; inflammatory diseases; autoimmune diseases; eye diseases (e.g., age-related macular degeneration) and cataracts; vaginitis; or studies of yogurt interference with antibiotic uptake.

Studies investigating conventional yogurt as either a single intervention or in combination with any other non-probiotic substance were eligible for inclusion. Studies that compared conventional yogurt with any non-probiotic yogurt, any non-yogurt substance, or placebo were also eligible. Studies of yogurt supplemented with probiotics, fermented milk products, such as kefir and kumys, fermented baby formula, or milk were not eligible for the scoping review.

Data Sources and Search Strategy

An extensive literature search was conducted during November 2013 in a range of relevant databases to identify studies investigating the health effects of yogurt. The search was limited to conventional yogurt as defined by the Codex Alimentarius international food standards for fermented milks (CODEX STAN 243-2003) (Codex Committee on Milk and Milk Products, 2010).

The full list of databases searched is included in Supplementary Table B. The searches were not limited by date or language. Information on ongoing or recently completed

studies, unpublished research, and research reported in the gray literature was identified by searching selected major relevant conference proceedings from the past 3 years. Gray literature was identified via OAISTER, OpenGray and NTIS. The search strategy involved only search terms for conventional yogurts, including many synonyms used in different parts of the world for this traditional foodstuff, as shown in the Medline search strategy (**Figure 1**).

Reference lists of relevant reviews, trials and studies were used to identify any additional studies that might be eligible for inclusion.

Study Selection

Record selection was undertaken using several passes. The first pass was undertaken by one reviewer (SB) in order to rapidly remove obviously irrelevant records such as research undertaken in animals or case reports. Second pass record selection was undertaken by two reviewers (JE, SB) independently, using the title and abstract of records. The full text of included studies was then assessed for relevance by one of the authors (JE) and checked by a second independent reviewer (SB). Discrepancies were resolved through discussion and where necessary by consulting a third reviewer.

Data Extraction

One researcher (JE) extracted selected data from the full papers of each of the included studies using a standardized template into an Excel spreadsheet, and a second researcher (SB) checked the extraction. In the absence of full paper copies or when only abstracts were available, data were extracted from the abstracts alone. Details of the information extracted from the included studies are listed in Supplementary Table C.

At the data extraction stage some studies, on closer inspection, proved ineligible. The number of records lost at this stage of the review process is documented in the PRISMA flow diagram (**Figure 2**).

RESULTS

A total of 17,024 records were identified by the searches and an additional 30 records through other sources. After de-duplication 10,684 records were taken forward for title and abstract screening. A further 9,903 records were excluded by the second pass, leaving 781 records for full text assessment. Of these 560 were excluded in the third pass leaving a total of 221 eligible studies. The number of studies identified by the searches at the various selection stages is reported in a PRISMA study flow diagram (**Figure 2**). Of these, 213 studies were available with either an English abstract or English full text and are included in the categorization. Studies available only as abstracts were included in this scoping review, because there was generally sufficient information to suggest potential eligibility.

We grouped study designs into broad categories for the purpose of this report, to provide information on the type of

1	yogurt/ (1356)
2	streptococcus thermophilus/ (500)
3	lactobacillus delbrueckii/ (239)
4	(yogurt$ or yogurt$ or yoghourt$ or yaourt$ or joghurt$ or yogourt$ or yaghourt$ or yahourth$ or yoghurd$ or joghourt$ or jogourt$).ti,ab. (2417)
5	(maas or amasi$1 or dahi$1 or da-hi$1 or dohi$1 or meesti$1 or perugu$1 or thayir$1 or thayiru$1 or mosaru$1 or curd$1 or matsun$1 or matsoon$1 or matsoun$1 or matzoun$1 or madzoon$1 or madzoun$1 or matson$1 or matsoni$1 or dadiah$1 or dadih$1 or stragisto$1 or q?zana$1 or dhahi$1 or dhaunro$1 or juju dhau$1 or rahmjoghurt$ or jameed$1 or zabadi$1 or labni$1 or lebni$1 or labneh$1 or m?st chekide$1).ti,ab. (1496)
6	(streptococcus adj3 thermophilus).ti,ab. (1318)
7	s thermophilus.ti,ab. (587)
8	(lactococcus adj3 thermophilus).ti,ab. (46)
9	l thermophilus.ti,ab. (5)
10	(lactobacillus adj3 delbruecki$).ti,ab. (762)
11	l delbruecki$.ti,ab. (314)
12	bulgaricus.ti,ab. (942)
13	or/1-12 (6063)
14	(letter or editorial or comment or case reports).pt. (2826899)
15	case report.ti. (156156)
16	animals/ not (animals/ and humans/) (3966245)
17	13 not (14 or 15 or 16) (4681)

FIGURE 1 | Medline search strategies to identify studies reporting the health benefits of yogurt.

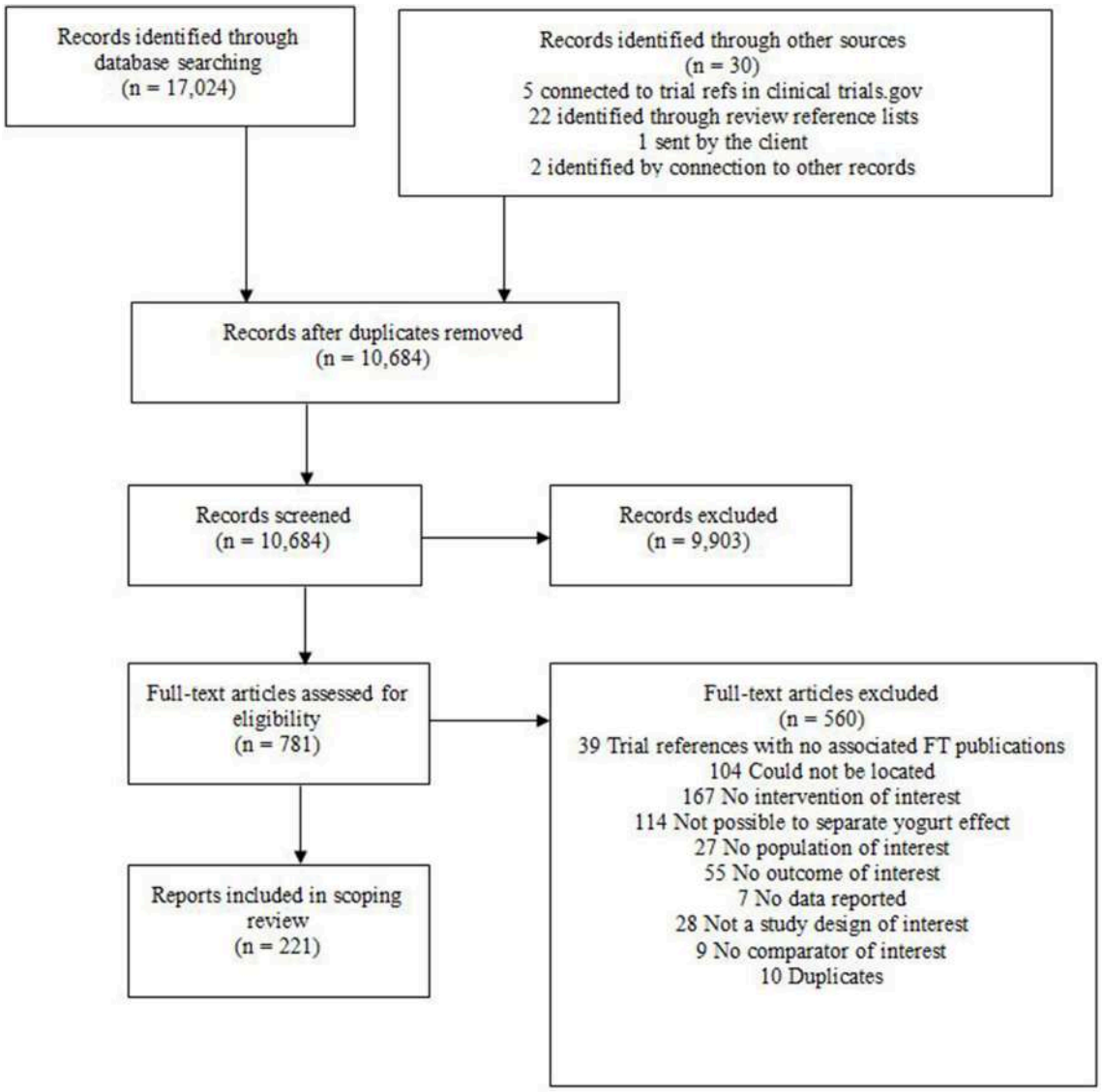

FIGURE 2 | PRISMA flowchart.

study, rather than the internal quality of the study. Generally, the RCTs, cohort studies (not population-based cohort studies) and cross-over trials had small study sizes, with 100 participants or fewer entering the studies. Cross-sectional studies and population-based (or large hospital-based) cohort studies had the largest study numbers, ranging from hundreds to tens of thousands of participants being enrolled. Case-control and case-cohort studies generally involved numbers of participants in the hundreds or thousands.

Reported Outcomes

The outcomes reported in eligible studies were: bone health (14 studies) (Motegi et al., 2001; Heaney et al., 2002; Berberidis et al., 2004; Sorenson et al., 2004; Arslantas et al., 2008; Jha et al., 2010; Uenishi and Nakamura, 2010; Bener and El Ayoubi, 2012; Nasrollahi et al., 2012; Sahni et al., 2012, 2013a,b; Bonjour et al., 2013; Feart et al., 2013), weight management and nutrition-related health outcomes (81 studies) (Jordan et al., 1981; Thompson et al., 1982; Bazzarre et al., 1983; Massey, 1984; McNamara et al., 1989; Sullivan et al., 1989; Rolls et al., 1991, 1994, 1995; Trapp et al., 1993; Vandewater and Vickers, 1996; Oosthuizen et al., 1998; Campbell et al., 1999, 2000; Burns et al., 2000, 2001, 2002; Hoffman et al., 2000; Zandstra et al., 2000; Mensink et al., 2002; Mossavar-Rahmani et al., 2002; O'Donovan et al., 2003; Rodriguez-Artalejo et al., 2003; Chien et al., 2004; Sorenson et al., 2004; King et al., 2005; Rosado et al., 2005; Yae et al., 2005; Zemel et al., 2005; Logan et al., 2006; Nobre et al., 2006; Tsuchiya et al., 2006; Albertson et al., 2007; Dewan et al., 2007, 2009; Diepvens et al., 2007, 2008; Nazare et al., 2007; Snijder et al., 2007; Beydoun et al., 2008; Bonet Serra et al., 2008;

Vergnaud et al., 2008; van der Zander et al., 2008; Almiron-Roig et al., 2009; Berkey et al., 2009; Jordão et al., 2009; White et al., 2009; Chapelot and Payen, 2010; Hursel et al., 2010; Keast et al., 2010, 2013; Lluch et al., 2010; Ortinau et al., 2010, 2012a,b, 2013; Pounis et al., 2010; Blom et al., 2011; Clegg et al., 2011; Jodkowska et al., 2011; Joshi et al., 2011; Margolis et al., 2011; Mozaffarian et al., 2011; Pordeus Luna et al., 2011; Schusdziarra et al., 2011; Smit et al., 2011; Thomas et al., 2011; Bener and El Ayoubi, 2012; Dougkas et al., 2012; Hogenkamp et al., 2012; Salakidou et al., 2012; Azadbakht et al., 2013; Buyuktuncer et al., 2013; Douglas et al., 2013; Meneton et al., 2013; Mensah and Otoo, 2013; Sazawal et al., 2013; Stritecka and Hlubik, 2013; Wang et al., 2013; Dawczynski et al., 2013; O'Connor et al., 2014), metabolic health (6 studies) (Snijder et al., 2007; Beydoun et al., 2008; Bonet Serra et al., 2008; White et al., 2009; Troy et al., 2010; Kim, 2013), cardiovascular health (57 studies) (Hepner et al., 1979; Rossouw et al., 1981; Thompson et al., 1982; Bazzarre et al., 1983; Jaspers et al., 1984; Massey, 1984; Cramer et al., 1989; McNamara et al., 1989; Sullivan et al., 1989; Freudenheim et al., 1991; Trapp et al., 1993; Oosthuizen et al., 1998; Iso et al., 1999; Mensink et al., 2002; Nakamura et al., 2002; Tavani et al., 2002; Steffen and Jacobs, 2003; Chien et al., 2004; Sorenson et al., 2004; Trautwein et al., 2004, 2005; Ganji and Kafai, 2004a,b; Steffen et al., 2005; Yae et al., 2005; Korpela et al., 2006; Rudkowska et al., 2007, 2008; Snijder et al., 2007; Bonet Serra et al., 2008; Masala et al., 2008; Niittynen et al., 2008; van der Zander et al., 2008; Wang et al., 2008, 2012, 2013; Dawczynski and Jahreis, 2009; Khandelwal et al., 2009; Larsson et al., 2009; Bonthuis et al., 2010; Sadrzadeh-Yeganeh et al., 2010; Clegg et al., 2011; Goldbohm et al., 2011; Ivey et al., 2011; Radler et al., 2011; Recio et al., 2011; Zhang et al., 2011; Amir Shaghaghi, 2012; Gouni-Berthold et al., 2012; Soedamah-Muthu et al., 2012; Azadbakht et al., 2013; Buyuktuncer et al., 2013; Javed et al., 2013; Kim, 2013; Meneton et al., 2013; Dawczynski et al., 2013), GI health (24 studies) (Niv et al., 1963; Dehesa et al., 1986; Porkka et al., 1988; Boudraa et al., 1989, 1990, 2001; Karabocuoglu et al., 1993; Trapp et al., 1993; Bhatnagar et al., 1998; Teuri and Korpela, 1998; Nakamura et al., 2000, 2001; Vazquez Martinez et al., 2005; Pashapour and Iou, 2006; Conway et al., 2007; Ranasinghe et al., 2007; Ballesta et al., 2008; Rafeey et al., 2008; Haenni et al., 2009; Pilipenko et al., 2009; Eren et al., 2010; Clegg et al., 2011; Frank et al., 2012; Isakov et al., 2013), cancer (39 studies) (Cook-Mozaffari et al., 1979; Le et al., 1986; Cramer et al., 1989; van't Veer et al., 1989; Peters et al., 1992; Kampman et al., 1994, 2000; Boutron et al., 1996; Shannon et al., 1996; Kocic et al., 1997; Ronco et al., 2002; Radosavljevic et al., 2003; Vlajinac et al., 2003; Juarranz Sanz et al., 2004; Kojima et al., 2004; Sakauchi et al., 2004; Sorenson et al., 2004; Kesse et al., 2005, 2006; Lin et al., 2005; Gallus et al., 2006; Genkinger et al., 2006; Mommers et al., 2006; Hsu et al., 2007; Janoutova et al., 2007; Matsumoto et al., 2007; Ornelas et al., 2007; Park et al., 2007; Heck et al., 2008; Kurahashi et al., 2008; Bonthuis et al., 2010; Karagianni et al., 2010; Djonovic and Arsenijevic, 2011; Pala et al., 2011; Faber et al., 2012; Kawakita et al., 2012; Reyhani et al., 2012; Duarte-Salles et al., 2013; Murphy et al., 2013), and diabetes (13 studies) (Nakamura et al., 2002; Sorenson et al., 2004; Choi et al., 2005; Liu et al., 2006; Kirii et al., 2009; Margolis et al., 2011; Dougkas et al., 2012; Sluijs et al., 2012; Soedamah-Muthu et al., 2012; Gheller et al., 2013; Grantham et al., 2013; Wang et al., 2013; O'Connor et al., 2014). Supplementary Tables D–J provide details of the studies identified in this scoping review for the outcomes of interest, presented in separate tables for each outcome category.

Twenty-two studies assessed other outcomes: Parkinson's disease risk (3 studies) (Chen et al., 2007; Miyake et al., 2011; Kyrozis et al., 2013), all-cause mortality (3 studies) (Bonthuis et al., 2010; Goldbohm et al., 2011; Soedamah-Muthu et al., 2012), skin complaints (3 studies) (Uenishi et al., 2004, 2008; Kim et al., 2010), respiratory complaints (3 studies) (Miyake et al., 2010, 2012; Maslova et al., 2012), joint pain/function (2 studies) (Martinez-Puig et al., 2013; Morina et al., 2013). The remaining 8 studies assessed a variety of other health outcomes: benign breast disease risk (Berkey et al., 2013), estrogen metabolism (Campbell et al., 1999), general mental/ psychological health (Crichton et al., 2010), minor health complaints (Hyland and Sodergren, 1998), immune function (Makino et al., 2010), general health (Mossavar-Rahmani et al., 2002), age of menarche (Ramezani Tehrani et al., 2013), and allergic symptoms (Trapp et al., 1993). Details of these studies are included in Supplementary Table K.

RCTs made up a large proportion of the weight management and nutritional health (23%), cardiovascular health (26%) and GI health studies (33%). Cross-sectional studies made up a large proportion of the weight management and nutritional health (18%), cardiovascular health (18%), metabolic health (50%) and bone health (50%) studies. Cohort studies made up a large proportion of the cancer (21%), cardiovascular health (26%), GI health (29%), other (41%), and diabetes (46%) studies. Cross-over trials were a common study design for cardiovascular health (19%) and weight management and nutritional (40%) health studies. Case-control and case-cohort studies were generally less common, although case-control studies were the most common study design in the cancer studies (59%) group.

We identified which studies might be similar enough to be suitable for combination in meta-analyses; details are included in Supplementary Table A.

DISCUSSION

Our scoping review shows that there is a substantial evidence base for investigating the health effects of conventional yogurt and that this evidence base is largest around weight management and nutrition-related health outcomes, cardiovascular health, GI health and cancer.

In principle, a systematic review with a narrative (textual) synthesis can be undertaken for outcomes with no evidence or little evidence, but when there is a larger evidence base there is greater opportunity for more robust assessments of effects. We suggest there are opportunities for meta-analyses among this evidence base where we have found studies that seem to be of similar design, investigating similar interventions and populations, and using the same outcome measures. The study population size is important, due to the inability to achieve significant results with small sample size.

Our results provide a useful evidence base for those interested in developing future nutritional interventions with conventional yogurt. Researchers planning new studies should ideally design them in the light of well-conducted systematic reviews (Al-Shahi Salman et al., 2014). This evidence base provides information which can both inform study design and provide the information for such systematic reviews. Based on this scoping review, three systematic reviews have already been undertaken: two of these included meta-analyses on the role of conventional yogurt in GI health in children (Patro-Golab et al., 2015a,b), and the third is ongoing and examines the effect of conventional yogurt on weight management outcomes.

Limitations of this Scoping Review

Studies only available as abstracts (e.g., conference abstracts) were included in this scoping review. Many of these studies would require further information from study authors to confirm their full eligibility to contribute to individual systematic review questions.

Some studies, particularly those by the same author(s) may contain the same, or part of the same, populations. As part of a full systematic review, duplicated or partly duplicated study populations would be identified and not pseudoreplicated. Because a scoping review involves only a high-level overview of study characteristics, we could not identify such duplicated populations with certainty, so there may exist a low degree of double counting in this scoping review.

Due to the limited level of data extraction undertaken in a scoping review, the assessment of the potential for combining studies in a meta-analysis must come with the *caveat* that some studies, especially those for which full study details were not available or reported may not, following assessment of the full study details, be eligible for meta-analysis. We highlight the need to contact authors where there is a lack of clarity about the eligibility of studies with respect to the design, population, intervention, comparator and/or outcomes. This scoping review did not assess the quality of eligible studies. In a full systematic review, the impact of including studies that are categorized with a high risk of bias may be explored in the meta-analyses via subgroup analyses.

The searches were conducted in November 2013. The volume of studies was such that processing took much longer than expected. However, the full strategies are presented in the supplementary files and this should make updating the scoping review relatively straightforward.

CONCLUSION

This scoping review identified a number of outcomes for which there exists substantial primary evidence that may be suitable for systematic review and potentially meta-analysis. Future systematic reviews of selected outcomes may provide further evidence for the health effects of yogurt consumption. Our results provide a useful evidence base for those interested in developing future nutritional interventions with conventional yogurt.

AUTHOR CONTRIBUTIONS

RS developed the idea for the study; JG designed the research. JE, JG, and SB conducted the research; JE and JG analyzed data. SB, JE, and JG co-wrote the report and the paper, with comments and edits from RS and HS. All authors take responsibility for final content. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fphar.2015.00246

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