FROST & SULLIVAN

Healthcare Cost Savings of Phytosterol Food Supplements in the European Union

Economic Implication of Managing Cardiovascular Disease with Phytosterol Food Supplements with Demonstrated LDL-cholesterol Reduction Capabilities

food supplements europe

An Independent Economic Analysis Commissioned by Food Supplements Europe

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Abstract

This case study explores the possible direct economic benefit that could be expected from the daily use of 1.7 grams of phytosterols – through fortified food sources or food supplements – as a means to reduce low-density lipoprotein (LDL) cholesterol concentration by those target individuals at the highest risk of developing cardiovascular disease (CVD). This report examines aggregated indications demonstrating that the use of phytosterols can potentially reduce CVD-attributed hospital utilisation costs in the European Union (EU) among those at a high risk of experiencing a costly, CVD-attributed event. Thus, a targeted phytosterol regimen is recommended as a means to help control rising societal healthcare costs and as a means for high-risk individuals to lower LDL-cholesterol and minimise the chance of having to deal with potentially detrimental disease-attributed events.

Target Population—31.1 million adults age 55 and older with severe hypercholesterolemia in the EU have an expected 24.3% risk of experiencing a costly CVD-attributed hospital event. The total cost of addressing CVD in the EU will be € 1,328 billion over the next 5 years, or € 34,637 per event over the same period.

Science-based Impact of Phytosterols Use—the relative risk of experiencing a CVD event is reduced by 26.6% for every 1 mmol/L reduction in LDL cholesterol levels, irrespective of how LDL-cholesterol is reduced. The expected reduction in LDL cholesterol levels given the use of 1.7 grams of a phytosterols food supplement daily is 0.372 mmol/L among severe hypercholesterolemic adults age 55 and older. This translates to an absolute risk reduction risk of 2.3% basis points given a 24.3% CVD-event risk level for the average European.

Economic Implications (Total EU)

- Total Avoidable CVD-attributed Costs per year (S): € 5.30 billion
- Net Avoidable CVD-attributed Costs per year (B): € 4.09 billion
- Net Avoidable CVD-attributed Costs per person per year (B/Pop): € 170.66 per target person
- Benefit/cost ratio (€ Avoided CVD-attributed Costs per € 1 spent on phytosterols): € 4.37

The Benefits of Phytosterols for LDL Cholesterol Reduction and Potential CVD Health Cost Savings

Background

Hypercholesterolemia is the presence of high total cholesterol levels in the blood and its presence is correlated to a higher risk of cardiovascular disease CVD[1] [1]. Cholesterol is a lipid-based substance present in all body cells and is delivered from foods from an animal origin including eggs, dairy products, meat, poultry, and fish and via endogenous synthesis. [1]. Cholesterol is required to build cell membranes, and it acts as a precursor of important molecules including hormones. However, consuming too much cholesterol can lead to a higher risk of developing CVD [1]. Thus, the consumption amount and the metabolism of cholesterol is primarily dependent on individual diet choices, it is considered by medical professionals as a modifiable risk factor for CV[6]. D that can be managed through a nutrition-based solution [1].

The cut-off level of hypercholesterolemia is 5.0 mmol/L of total cholesterol according to the World Health Organization (WHO); however, severe hypercholesterolemia is 6.2 mmol/L of total cholesterol [5]. According to the 2016 ESC/EAS Guidelines for the Management of Dyslipidemias, treatment with an intense dose of statins is recommended for male patients age 55 and older with CVD and female patients age 60 and older with CVD, or any patient with a baseline low-density lipoprotein (LDL) cholesterol level of greater than 5 mmol/L, should be treated with an intense dose of statins [6]. A healthy diet and lifestyle are the cornerstones of CVD prevention and should be followed irrespective of concomitant drug treatment. Phytosterols are recommended for both: individuals with high cholesterol levels at intermediate or low global CVD risk who do not qualify for pharmacotherapy and as an adjunct to pharmacologic therapy in high and very high risk patients who fail to achieve LDL-cholesterol target levels on statins or are statin-intolerant [19]. The presence of cholesterol, or more specifically, higher concentrations of LDL cholesterol and lower concentrations of functional high-density lipoprotein (HDL) cholesterol, promotes the development of plaque in the arteries that leads to blood flow restriction [1]. The average LDL cholesterol level of someone with severe hypercholesterolemia is approximately 4.8 mmol/L based on a fixed LDL cholesterol to HDL cholesterol ratio of 3.4 for someone at an average risk of experiencing a CVD event [2].

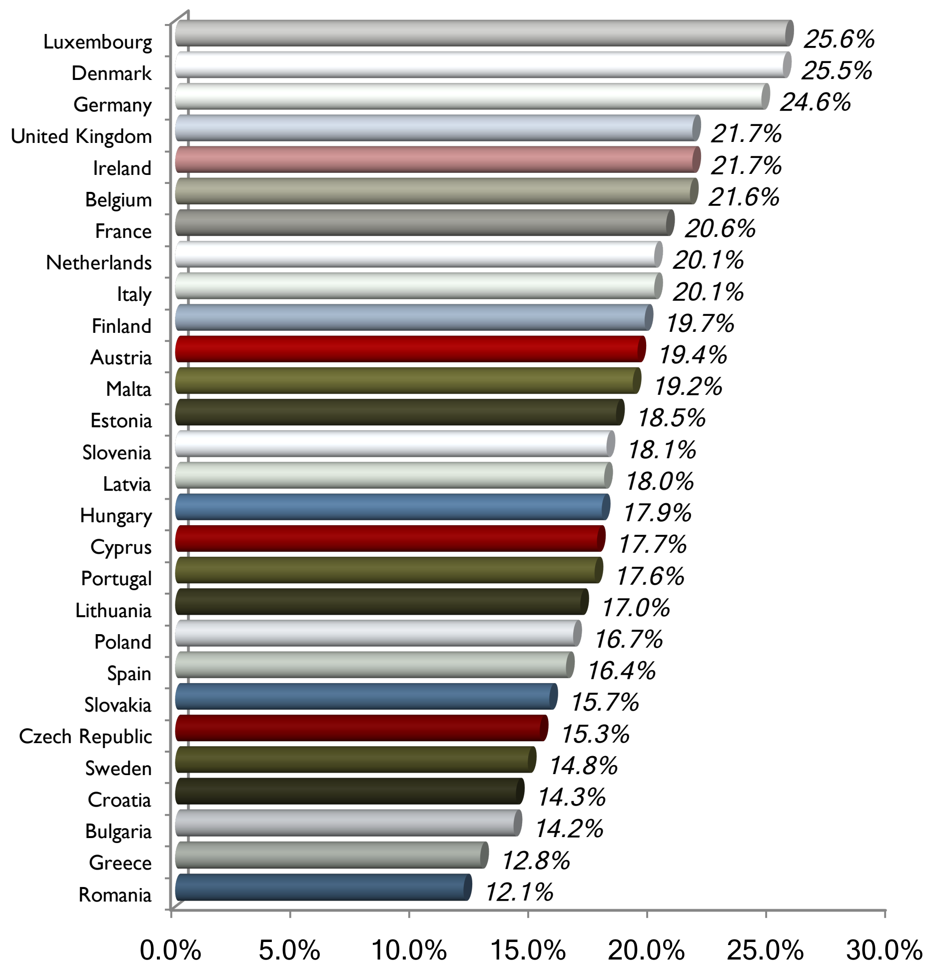
The presence of cholesterol promotes the development of plaque in the arteries that leads to blood flow restriction and can in turn increase the risk of experiencing a CVD-attributed medical event.

1 CVD is strictly defined as events associated with the following ICD/ISHMT codes: 0901 (hypertensive diseases), 0902 (angina pectoris), 0903 (acute myocardial infarction), 0904 (other ischaemic heart disease), 0907 (heart failure), 0908 (cerebrovascular diseases), and 0909 (atherosclerosis) [4]. The choice of ISHMT codes reflects the author's conservative judgment that these events are nearly always associated with CVD as the main underlying or direct cause.

According to the WHO's Global Health Observatory (GHO) statistics, Europe has the highest prevalence of hypercholesterolemia in the world, at 54% of the total population age 25 and older, and 20% of the total population has severe hypercholesterolemia [3]. It is expected that the prevalence of hypercholesterolemia is greater among Europeans age 55 and older, however exact figures for the entire EU for this target population cohort, and the prevalence of hypercholesterolemia - for this target population cohort per EU country is not currently known. Thus, a conservative measure of the prevalence of hypercholesterolemia was adopted for the purposes of this case study.

See Chart 1 for the percent of the population age 25 and older with severe hypercholesterolemia (6.2 mmol/L) per EU country. See Table 1 for estimated mean total cholesterol, LDL cholesterol levels by EU country, and the share of the population with severe hypercholesterolemia by EU country.

Chart 1
Percent of the Population age 25 and older with Very High Total Cholesterol Baseline Levels (6.2 mmol/L) per EU Country, %, 2015
EU Average: 19.7% of Total Population



Source: World Health Organization, Global Health Observatory and Frost & Sullivan analysis.

Table 1
Total Burden of Cardiovascular Disease: Mean Total Cholesterol and LDL Cholesterol Levels by EU country, 2009

Country	Mean Total Cholesterol Level[2]	Expected LDL cholesterol Baseline Level[3]	% of Population age 25 and older with Severe Hyper- cholesterolemia)[4]
Austria	6.0	4.6	19.4
Belgium	6.1	4.7	21.6
Bulgaria	5.8	4.4	14.2
Croatia	5.8	4.4	14.3
Cyprus	5.9	4.6	17.7
Czech Republic	5.5	4.2	15.3
Denmark	6.1	4.7	25.5
Estonia	6.0	4.6	18.5
Finland	5.7	4.4	19.7
France	5.8	4.4	20.6
Germany	5.4	4.2	24.6
Greece	5.6	4.3	12.8
Hungary	6.0	4.6	17.9
Ireland	6.1	4.7	21.7
Italy	5.8	4.4	20.1
Latvia	6.0	4.6	18
Lithuania	6.0	4.6	17
Luxembourg	6.2	4.8	25.6
Malta	6.0	4.6	19.2
Netherlands	6.0	4.6	20.1
Portugal	5.7	4.4	17.6
Poland	5.9	4.5	16.7
Romania	5.9	4.5	12.1
Slovakia	5.9	4.5	15.7
Slovenia	6.0	4.6	18.1
Spain	5.9	4.5	16.4
Sweden	5.5	4.3	14.8
United Kingdom	6.0	4.6	21.7
Total EU	**5.7**	**4.4**	**20.3**

Europe has the highest prevalence of hyper-cholesterolemia (5.0 mmol/dL) in the world, at 54% of the total population, and 20% of the total EU population has severe hyper-cholesterolemia (6.2 mmol/dL).

2 World Health Organization. Global Health Observatory (GHO) data. Retrieved at: http://gamapserver.who.int/gho/interactive_charts/ncd/risk_factors/cholesterol_mean/atlas.html. Includes the average of both female and male findings age 25 and older
3 In order to determine the expected LDL cholesterol concentration per country from the observed mean total cholesterol levels, the authors used the fixed LDL cholesterol to HDL cholesterol ratio of 3.4 for someone at an average risk of experiencing a CHD event (http://www.exrx.net/Testing/LDL%26HDL.html.). This implies that the expected LDL-concentration is approximately equal to (3.4*Mean Total Cholesterol)/(1 + 3.4).
4 Severe Hypercholesterolemia is ≥ 6.2 mmol/L.

Among adults age 55 and older in the EU, 24% of this target population will experience a CVD-attributed hospital event over the next 5 years.

For the purposes of this case study on the use of phytosterols, event risk is defined as the ratio of the total number of observed CVD-attributed outcomes requiring a set of hospital services observed in a given population relative to the total target population. In other words, an event is defined as a person experiencing an CVD-attributed event that requires professional medical attention and, consequently, hospital service utilisation such as outpatient or office-based provider visits, hospital inpatient stays, emergency room visits, prescribed medications, and home care such as home nursing and medical devices used at home [4]. It should be noted that the dataset used for this analysis is seemingly implying that the correlation between CVD event rate per EU country (the ratio of cumulative number of hospital events relative to total population age 55 and over) and the mean total cholesterol levels per EU country is not statistically significant. But because each EU country was treated as its own case study, this comparison ignores many factors that determine the differences in the risk of CHD in a given country which was not controlled for in this study.

According to hospital utilisation statistics provided by the World Health Organization, Regional Office of Europe as first reported in the Food Supplements Europe economic case study of the benefits of omega-3 utilisation, over 38.0 million CVD-attributed hospital events occurred from 2011 to 2015 in the EU among adults age 55 and older as defined by the aforementioned ICD/ISHMT codes [5, 7]. Thus, each individual adult age 55 and older in the EU has a one in four chance of experiencing a CVD-attributed event requiring formal and informal heath care services over the next five years. These CVD-attributed events include both primary and secondary CVD cases. In other words, it is expected that a total of 38.4 million CVD-attributed hospital events are expected over the next 5 years (2016 to 2020) among adults age 55 and older in the EU, or 24% of the target population will experience a CVD-attributed hospital event [5, 7]. Growth trends in CVD-attributed events by EU country does vary by a number of reasons such as target market population growth, quality-of-care by EU country, and general health of the target population which was controlled for when projecting CVD-attributed events over the next five years. Table 2 shows the social burden of CVD on the EU population by nation.

Table 2
Burden of Cardiovascular Disease: CVD-attributed Event Risk, 2011-2020[5,6]

Country	Total Population, age 55 and older [7]	Total Population, age 55 and older with Severe Hypercholesterolemia	Expected Event rate (Risk)	Expected Number of CVD events among Target Population[7]
Austria	2,574,872	499,525	38.2%	196,959
Belgium	3,378,041	729,657	21.9%	148,174
Bulgaria*	2,395,715	340,192	31.3%	149,911
Croatia*	1,366,757	195,446	23.5%	64,364
Cyprus	217,517	38,501	3.6%	1,570
Czech Republic	3,224,578	493,360	27.4%	176,680
Denmark	1,705,383	434,873	17.9%	61,056
Estonia*	408,180	75,513	27.1%	22,162
Finland	1,801,776	354,950	24.2%	87,374
France	20,023,397	4,124,820	18.6%	744,430
Germany	27,840,013	6,848,643	38.2%	2,126,100
Greece	3,544,810	453,736	20.6%	146,132
Hungary	3,107,068	556,165	31.7%	197,073
Ireland	1,051,651	228,208	26.4%	55,568
Italy	20,248,958	4,070,041	19.4%	785,117
Latvia	630,755	113,536	26.3%	33,116
Lithuania	900,267	153,045	64.7%	116,574
Luxembourg	139,939	35,824	27.2%	7,603
Malta	134,864	25,894	17.0%	4,580
Netherlands	5,078,117	1,020,702	16.6%	168,431
Portugal	3,233,995	2,003,132	22.9%	148,337
Poland	11,381,429	540,077	32.1%	731,401
Romania	5,966,193	721,909	30.8%	367,357
Slovakia	1,455,578	228,526	35.2%	102,584
Slovenia	647,904	117,271	22.4%	29,080
Spain	13,719,534	2,250,004	13.9%	382,424
Sweden	2,992,914	442,951	20.6%	123,034
United Kingdom	18,426,690	3,998,592	13.4%	493,429
Total EU	**157,596,895**	**31,095,091**	**24.3%**	**7,670,620**

Source: [4] European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis and Frost & Sullivan

5 [8] Eurostat. European Commission (http://ec.europa.eu/eurostat/data/database)
6 [5] The World Health Organisation, Regional Office of Europe and Frost & Sullivan analysis
7 Calculated by taking the product of the expected event rate (Risk) and the total population, age 55 and older with severe hypercholesterolemia. All figures are rounded.

Total expenditures of addressing medical events requiring a mix of hospital services for all EU adults age 55 and older is expected to be € 1,328 billion over the next 5 years, or approximately € 265.7 billion per year.

Total expenditures of addressing medical events requiring a mix of hospital services for all EU adults age 55 and older is expected to be € 1,328 billion over the next 5 years, or approximately € 265.7 billion per year after controlling for purchasing power parity across each country within the EU [4,5, 10]. A significant portion of this cost is related to events that require expensive hospital care services, especially inpatient procedures and emergency room visits. This cost also includes treatment-specific pharmaceuticals, outpatient visits, and informal costs such as post-treatment home/nursing care services. Furthermore, there are significant indirect costs of CVD on society as a whole including less productivity income for the state due to CVD-attributed deaths. Table 3 shows the costs of CVD for the EU population by country.

The average cost of a CVD-attributed hospital event in the EU will be € 34,637 per event [4, 9][8]. The average cost of each CVD-attributed event is calculated by taking total expenditure over the next 5 years and dividing it by the cumulative number of events. This cost calculation approach was adopted because some CVD-attributed events and its residual post treatment disease management costs may stretch beyond one year for a given event. For example, the cost of inpatient care, which is the expenditure for care of patients who requires hospital admission at the beginning of the CVD-attributed event, and post-treatment informal costs such as home nurses, medical equipment for home use and lost productivity which is typically spent over several months or years after the initial event are nearly equal in share of cost burden at 32.9% each. The cost of medications for managing CVD makes up an additional 19.1% of the financial burden of CVD. The remaining services contributing to CVD-attributed healthcare costs make up a combined 15.1% of the cost burden and include primary care (5.7%), outpatient care (8.3%) and ambulance and emergency (A&E) (1.1%). For details on the average annual cost of a CVD-attributed hospital event by cost component for the total EU and the annual cost of a CVD-attributed hospital event by cost component by selected EU countries, see Appendix 2.

8 European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis, Frost & Sullivan. The average cost of each CVD-attributed event is calculated by taking total expenditure over the next 5 years and dividing it by the cumulative number of events. This event cost was taken because some events and its residual post treatment disease management costs may stretch beyond one year for a given patient.

Table 3
Total Burden of Cardiovascular Disease: CVD-attributed Event Costs, 2016-2020

Country	Average Annual Cost of CVD-attributed Hospital Event, € /event [4,8][9]	h: Adjusted Average Annual Cost of CVD-attributed Hospital Event, € /event[10]	Adjusted Average Annual Cost of CVD-attributed Hospital Events[6]
Austria	€ 27,683	€ 28,248	€ 5,563,689,141
Belgium	€ 25,422	€ 25,422	€ 3,766,879,931
Bulgaria	€ 13,493	€ 29,684	€ 4,449,944,019
Croatia	€ 16,666	€ 30,555	€ 1,966,649,272
Cyprus	€ 42,229	€ 51,613	€ 81,040,635
Czech Republic	€ 14,384	€ 26,371	€ 4,659,228,314
Denmark	€ 39,916	€ 31,362	€ 1,914,830,363
Estonia	€ 10,861	€ 17,068	€ 378,269,071
Finland	€ 32,954	€ 30,208	€ 2,639,397,093
France	€ 37,304	€ 41,034	€ 30,546,939,340
Germany	€ 33,921	€ 37,313	€ 79,331,165,848
Greece	€ 27,666	€ 38,041	€ 5,558,991,998
Hungary	€ 7,224	€ 13,244	€ 2,610,030,846
Ireland	€ 57,865	€ 57,865	€ 3,215,470,206
Italy	€ 32,361	€ 35,597	€ 27,947,817,630
Latvia	€ 15,298	€ 24,040	€ 796,105,211
Lithuania	€ 6,424	€ 11,777	€ 1,372,897,126
Luxembourg	€ 31,284	€ 28,677	€ 218,037,429
Malta	€ 27,954	€ 38,436	€ 176,030,706
Netherlands	€ 49,663	€ 49,663	€ 8,364,780,897
Portugal	€ 27,666	€ 33,814	€ 5,015,879,512
Poland	€ 22,808	€ 41,814	€ 30,582,781,633
Romania	€ 13,493	€ 29,684	€ 10,904,621,372
Slovakia	€ 8,660	€ 13,609	€ 1,396,067,143
Slovenia	€ 16,666	€ 22,916	€ 666,396,987
Spain	€ 33,823	€ 41,339	€ 15,809,040,425
Sweden	€ 27,666	€ 23,410	€ 2,880,224,373
United Kingdom	€ 31,318	€ 26,099	€ 12,878,000,037
Total EU	**€ 29,118**	**€ 34,637**	**€ 265,691,206,557**

The average cost of a CVD-attributed hospital event in the EU will be € 34,637 per event.

9 European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis, Frost & Sullivan
10 Average annual cost of CVD-attributed hospital event, € /event adjusted for purchasing power parity (PPP) ratios provided by the World Bank. See Table 7 in this report or [10] http://data.worldbank.org/indicator/PA.NUS.PPPC.RF for the PPP ratios

Any intervention, including a nutrition-based regimen that is shown to reduce a person's LDL cholesterol level, ought to also help reduce the odds of experiencing a costly CVD event.

The Health Benefits of Phytosterols

Current treatment guidelines state that LDL cholesterol should be the primary target of therapy, since the main substrate for atherosclerotic plaque formation is oxidised LDL particles. It has been shown that different methodologies of cholesterol reduction (inhibiting cholesterol absorption or cholesterol synthesis) can lead to a reduction in the risk of coronary artery disease event rate [11, 12, 13, 14]. It had been predicted that a 1% reduction in LDL cholesterol reduces the risk of coronary artery disease by 1.2–2.0% [15]. Also, in a meta-analysis of the effects of LDL cholesterol concentration reduction on the risk of coronary artery disease by Gould et al. (2007), it was estimated that a 1 mmol/L (38.7 mg/dl) reduction in LDL cholesterol provides a 26.6% decrease in the relative risk of experiencing any CHD-related event and a 28.0% decrease in the relative risk of a CHD-attributed death [16]. Thus, any intervention, including a nutrition-based regimen that is shown to reduce a person's LDL cholesterol level, ought to also help reduce the odds of experiencing a costly CVD event.

One such nutrition-based regimen that has shown significant promise in lowering LDL cholesterol levels is the daily use of phytosterols. Phytosterols[11] are structurally related to cholesterol found in animals and are present in high concentrations in vegetable oils and nuts [17, 18, 19]. There are many types of phytosterols, of which beta-sitosterol and campesterol are among the most abundant. Phytosterol consumption has been shown to lower LDL cholesterol levels through a mechanism of action in which phytosterols hinder cholesterol absorption in the digestive tract. Because of the strong connection to reducing cholesterol levels, the European Food Safety Authority (EFSA) has assessed positively health claims for the consumption of phytosterols as part of a diet that reduces blood cholesterol levels [20, 21]. EFSA scientists stated in an Opinion, and supported by Regulations (EC) No 983/2009 and (EU) No 384/2010, that LDL cholesterol can be reduced by 7 to 10 % within two to three weeks on average if a person consumes 1.5 to 2.4 grams of phytosterols per day [20, 21]. In addition, the European Atherosclerosis Society (EAS) Consensus Panel states that when plant sterols and stanols are taken at 2 g/day there is casual significant inhibition of cholesterol absorption and lowers LDL cholesterol levels by between 8 and 10%, leading the Panel to conclude that phytosterols are a potent dietary option available for reducing LDL cholesterol levels.

11 Phytosterols comprise of both plant sterols and plant stanols.

Multiple meta-analyses that explore both the expected health benefits, and consequential financial impact, from the use of phytosterols and resulting reduction of LDL cholesterol levels have been conducted over the last decade. In their clinical and financial impact analysis, Phillips, Belsey, and Shindler found that the daily use of products with added 1.6 grams of phytosterols by individuals with high cholesterol levels in the UK reduced total cholesterol levels by 5.9% and LDL cholesterol levels by 8.5% [22]. Based on the connection between lower LDL-levels and the decrease of CVD events, these reductions might in turn reduce overall CVD event risk and CVD-attributed costs at an expected rate of £86 million per year. Gerber et al. (2006) substantiated these findings with their review of the potential healthcare cost reduction that could be realised in Germany if those with high cholesterol blood levels daily used phytosterols. Their analysis amounted to a total of 117,000 CVD cases over 10 years and a cost reduction of 1.3 billion over the same period [23]. In 2013, Shanahan and de Lorimier reviewed the phytosterol health literature and calculated the potential health care cost savings that could be realised by people with high cholesterol in the United States [24]. It was found that the expected relative risk reduction of a CHD-related medical event, given the regular use of phytosterols among the target population of US adults age 55 and over was 11.2%, which implied an annual average of 283,389 avoided events from 2013 to 2020 and that 2,267,111 cumulative avoided events over that period could be expected [24].

The EFSA recommendation of the use of 2.0 grams per day of phytosterols/ phytostanols will yield an expected reduction of LDL-cholesterol of 8.4%.

A recent meta-analysis that looks at the potential health benefits that can be derived from the daily use of phytosterols was the work of Ras, Geleijnse, and Trautwein in 2014, which specifically evaluated the expected effects of phytosterol use across a spectrum of regimen levels on LDL cholesterol levels [25]. In this work, a total of 124 clinical studies were systematically analyzed. The average phytosterol daily usage amount across all of the studies was 2.1 grams per day. The weighted results show that the observed average reduction in LDL cholesterol levels at the average daily usage amount of 2.1 grams was 8.4% of baseline when compared to a placebo. Also, the effects do vary by daily usage amount as shown in Chart 1 and Table 4, where the observed reduction in LDL cholesterol levels was 5.7% for the subset of clinical studies that tested daily usage amounts of one gram per day or less and the observed reduction in LDL cholesterol levels was 12.4% for the subset of clinical studies that tested daily usage amounts more than three grams per day [25]. The strength of the correlation between the average reduction of LDL cholesterol (%) and average phytosterol use (g/d) is very strong ($R^2 > 0.99$) and implies that the EFSA recommendation of 2.0 grams per day of phytosterols will yield an expected reduction of LDL cholesterol of 8.4%.

For the purposes of this case study, the risk-reducing activity is the daily intake of 2.0 grams of phytosterols per day which is expected to result in a 8.4% reduction in the observed in LDL cholesterol levels based on the work of Ras, Geleijnse, and Trautwein (2014) [25]. However, the average person in the EU acquires 300 mg of their required phytosterol intake from their diet [25]. This means that the average person has an expected 1.7 grams phytosterol intake deficiency that could be addressed with a phytosterol supplement.

Chart 1
Average Reduction of LDL cholesterol (%) as a Function of Average Phytosterol Use (g/d)

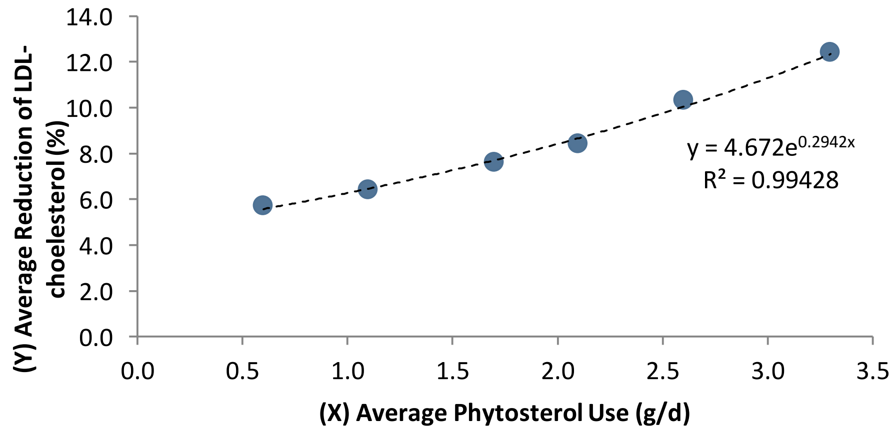


Table 4
Average Reduction of LDL cholesterol (%) as a Function of Average Phytosterol Use (g/d)

Study Arms Category	Average Phytosterol and Phytostanol Use (g/d)	Average Reduction of LDL-choelesterol (%)
1	0.6	5.7
2	1.1	6.4
3	1.7	7.6
4	2.1	8.4
5	2.6	10.3
6	3.3	12.4
EFSA recommendation	2.0	8.4
adjusted-EFSA recommendation	1.7	7.7

Source: [25] Ras, Geleijnse, and Trautwein (2014)

Research Methods

This case study explores the possible direct economic benefit that could be expected from the daily use of 1.7 grams of phytosterols – through fortified food sources or food supplements – as a means to reduce LDL cholesterol concentration by those target individuals at the highest risk of developing CVD. Specifically, a review of the scientific literature related to phytosterol intake and its possible effect on reducing LDL cholesterol levels is provided. Furthermore, this case study deduces the expected financial benefits for people with elevated blood cholesterol levels using phytosterols and provides the expected economic benefit equivalent for EU-based healthcare payer decision makers.

The health economic analysis presented in this case study is based on the assessment of various cost scenarios and determines the difference between scenarios to derive the potential savings, or loss, that occurs if one scenario of events occurred versus another [24]. The benefits considered in this model are avoided medical expenditures related to avoided CVD-attributed medical care service utilisation through the adoption of a risk-reducing activity (***S***). All calculated monetary benefits derived from this analysis will be adjusted downward to reflect the 300 mg of phytosterol intake addressed through diet. and the use of phytosterol-fortified foods [26]. The result of these potential healthcare savings provides an economic indication of the monetary benefits the user of phytosterols food supplements can yield for all of society through medical cost reduction and increased productivity.

Table 5 provides a list of the key variables used to conduct this health economic analysis.

Table 5

List of Key Variables used in this Economic Analysis**A**	Number of possible avoided events (A) if everybody in the target population of adults age 55 and older with severe hypercholesterolemia used phytosterol
B	Total potential net economic benefits yet to be realised from the daily use of phytosterols
B/Pop	Net Benefit per User
C	Total cost of a phytosterol regimen
d	The expected per person cost of phytosterol utilisation per year
h	The expected cost of a CVD-attributed medical event
N*	Absolute Risk Reduction
Pop	Target Population: Adults age 55 and older with severe hypercholesterolemia
$Risk_x$	Risk of a CVD event
RR_{x-1}/RRx	Relative risk of a CVD event given a 1 mmol/L (38.7 mg/dL) reduction in LDL cholesterol
δ	Mean reduction in serum LDL cholesterol (mmol/L) concentration achieved through the consumption of phytosterols
S	Total potential savings from reduced hospital service utilisation following CVD-attributed hospital events that are realisable if the entire target population of adults age 55 and older with severe hypercholesterolemia were to sufficiently utilise 2.0 grams of phytosterols per day
S/C	Total Benefit Cost Ratio
S/Pop	Total Benefit per User

Source: Frost & Sullivan analysis

Reducing serum LDL cholesterol concentration reduces the risk of coronary artery disease—it had been predicted that a 38.7 mg/dL reduction in LDL cholesterol reduces the risk of coronary artery disease by 26.6%.

In this case study, the following two scenarios are compared: A) the non-use of phytosterols and B) 100% utilisation of phytosterols among a specified population. The difference in total expected health care costs between the two scenarios is the total potential net savings (or loss) that is possible through 100% utilisation of phytosterols. The difference between the two scenarios is also the total number of avoidable events that is possible if everyone used phytosterols at cholesterol lowering levels. In order to determine the number of CVD events between the two states, a measure of the relative risk (*RR*) of these two event states can be used to determine the number of people who would need to use phytosterols in order to realise its benefit. If the relative risk reduction measure is known, then an absolute risk reduction given the risk profile of a predetermined target population can be determined.

For the purposes of this case study, *N** is absolute risk reduction and ***N**** can be expressed as:

$$1. \qquad N^* = Risk_x \left(1 - \left(\frac{RR_{x-1}}{RR_x}\right)^{\delta}\right)$$

where the term $\left(\frac{RR_{x-1}}{RR_x}\right)^{\delta}$ is the ratio of the relative risk of a CVD event between a user of phytosterols versus a non-user. Specifically, the term RR_{x-1}/RR_x is the relative risk of a CVD event given a 1 mmol/L (38.7 mg/dL) reduction in LDL cholesterol. According to Gould et al (2007), the relative risk of experiencing a CVD event was found to be reduced by 26.6% for every 1 mmol/L reduction in LDL cholesterol [12]. The expression δ is the mean reduction in serum LDL cholesterol (mmol/L) concentration achieved through the consumption of phytosterols. As stated above, the work of Ras, Geleijnse, and Trautwein (2014) implies that the mean reduction in serum LDL cholesterol (mmol/L) concentration achieved through the consumption of 2.0 grams of phytosterols per day was 8.4% [25]. However, as stated above, the average person in the EU acquires 300 mg of their required phytosterol intake from their diet [25]. This means that the average person has an expected 1.7 grams phytosterol intake deficiency that could be addressed with a phytosterol supplement. Using the relationship equation in Table 4, then the adjusted mean reduction in serum LDL cholesterol (mmol/L) concentration achieved through the consumption of 1.7 grams of phytosterols per day is 7.7% Assuming that the baseline total cholesterol levels of 6.2 mmol/L and the expected baseline LDL cholesterol levels of 4.8 mmol/L is considered severe hypercholesterolemic, then the mmol/L equivalent of the decrease in LDL cholesterol levels given the use of phytosterols is 0.372 mmol/L.[12] See the Appendix for a detailed explanation of the calculations used to derive the relative risk estimates used in this case study.

12 The general calculation of this figure is based on the product of the baseline LDL cholesterol level (4.8 mmol/L) and the expected decrease in LDL cholesterol of 8.4%.

Overall, adults age 55 and older in the European Union with high LDL cholesterol base levels face a 24.3% chance of experiencing a CVD event. Based on an application of equation 1, it is expected that given the daily intake of 2.0 grams of phytosterols, this risk can be reduced by 2.3% basis points. However, the potential absolute risk reduction of a given country varies due to the level of CVD risk the citizens of these countries face. For example, adults age 55 and older in Lithuania with high LDL cholesterol levels face a very high risk of experiencing a CVD event—consequently the potential health benefits of using a phytosterol supplement is much greater.

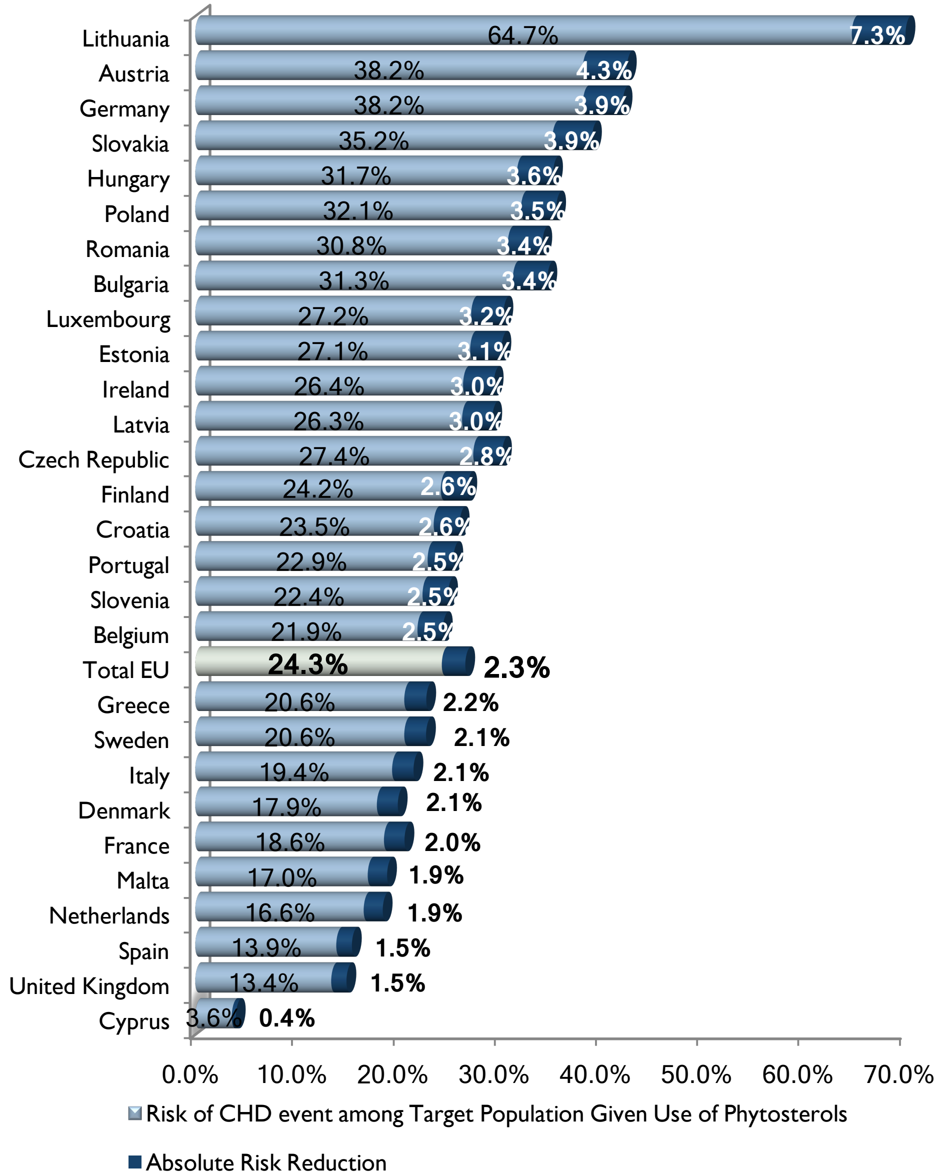
Overall, the 2.3% absolute risk reduction corresponds to 170,542 possible CVD-attributed hospital events that could be avoided throughout the European Union per year. However, likely risk reduction benefits from using phytosterols per day varies by EU country based on the observed CVD-attributed event rates of each country. For example, the absolute risk reduction in Lithuania is 7.3% and in Austria it is 4.3%, because each country's population has a relatively high risk of experiencing a CVD-attributed event. Table 6 and Chart 2 provide the CVD risk descriptive statistics used in this case study.

Phytosterol consumption has been shown to lower LDL cholesterol baseline levels through a mechanism of action in which phytosterols hinder cholesterol absorption in the digestive tract.

Given the daily intake of 2.0 grams of phytosterols, CVD-event risk can be reduced by 2.7% basis points, or can lead to 170,542 possible CVD-attributed hospital events throughout the European Union per year.

Chart 2

Risk of a CVD-attributed Event and the Absolute Risk Reduction Potential per Target User, EU, 2015



Note: The EU weighted average absolue rsk reduction (2.3%) is calculated by taking a weighted average of the absolute risk reductions by the total target population (Total Population, age 55 and older with Severe Hypercholesterolemia). Source: Author calculations based on the findings of [25] Ras, Geleijnse, and Trautwein (2014), [16] Gould et al (2007), [8] Eurostat, and the [5] World Health Organisation

Table 6
CVD Benefits from Phytosterol Use: Average Expected Relative Risk Measurements by EU Country, 2015

Country	N*: Absolute Risk Reduction Indicator	Pop x N* = A: Annualised Average # of Avoided CVD-attributed Events from use of Phytosterol Supplements, 2016 - 2020[13]
Austria	4.3%	4,206
Belgium	2.5%	3,953
Bulgaria	3.4%	1,648
Croatia	2.6%	717
Cyprus	0.4%	27
Czech Republic	2.8%	2,143
Denmark	2.1%	2,288
Estonia	3.1%	430
Finland	2.6%	1,833
France	2.0%	17,218
Germany	3.9%	66,085
Greece	2.2%	1,262
Hungary	3.6%	3,554
Ireland	3.0%	1,496
Italy	2.1%	17,288
Latvia	3.0%	609
Lithuania	7.3%	1,896
Luxembourg	3.2%	292
Malta	1.9%	95
Netherlands	1.9%	3,861
Portugal	2.5%	2,292
Poland	3.5%	12,247
Romania	3.4%	2,979
Slovakia	3.9%	1,401
Slovenia	2.5%	536
Spain	1.5%	5,698
Sweden	2.1%	1,408
United Kingdom	1.5%	13,079
Total EU	**2.3%[14]**	**170,542**

Source: Author calculations based on the findings of [25] Ras, Geleijnse, and Trautwein (2014), [16] Gould et al (2007), [8] Eurostat, and the [5] World Health Organisation

[13] Target Population is all adults age 55 and older with sever hypercholesterolemia levels, which is assumed to be approximately 20% of the EU population.

[14] 2.3% is calculated by taking a weighted average of the absolute risk reductions by the total target population (Total Population, age 55 and older with Severe Hypercholesterolemia).

Empirical Results

The potential savings from reduced medical care service utilisation following CVD events, ***S*** that is realisable if the entire target population were to utilise a phytosterol regimen at cholesterol lowering levels can be expressed as:

$$2.\ S = h * A = h * Pop * N^{*} = h * A * Risk_x \left(1 - \left(\frac{RR_{x-1}}{RR_x}\right)^{\delta}\right)$$

The term ***h*** is the expected per-person cost of a CVD event and ***A*** is the number of possible avoided events if everybody in the target population of adults age 55 and older with severe hypercholesterolemia used a phytosterols regimen per year. ***A*** is calculated by taking the product of the absolute risk reduction indicator ***N**** and the target population ***Pop*** (Adults age 55 and older with severe hypercholesterolemia). For the purposes of this case study, we are interested in the total potential cost savings between the extreme scenarios of non-use and 100% use, thus the removal of current users would be necessary to determine the proportion of health benefits already realised by current phytosterol users and the proportion of non-users yet to realise the benefits of phytosterols. An easy way to do this is to observe the population's purchasing behavior through consumer research and identify only those who have purchased phytosterols. The cumulative net savings achieved over consecutive years can also be calculated by summing the annual output over the indicated years while discounting future years to their present value.

There is a cost of using phytosterols that must also be considered. The net benefits that can be realised from avoided CVD-attributed medical events are:

$$3.\ B = S - C = (h * A) - (Pop * d)$$

where ***S*** is the total potential savings from reduced hospital service utilisation following avoided CVD-attributed medical events that are realizable if the entire target population were to sufficiently utilise phytosterols daily and the cost of phytosterol utilisation is represented by the parameter ***C.*** The total cost of a phytosterol regimen, assuming 100% utilisation by the entire observed population can be represented by ***C = Pop*d*** where ***d*** is the expected per person cost of phytosterol utilisation per year. Note that the entire target population of adults age 55 and older with severe hypercholesterolemia must take the given regimen in order for the total number avoided events to be realised. The result of this calculation provides an economic indication of the net monetary benefits ***B*** that the use of phytosterols can yield for society through hospital cost reduction and increased productivity due to avoided bed rest and loss of life.

The purchase and utilisation of phytosterols is required to capture these potential cost savings from avoided CVD-attributed medical events.

Also, it should be noted that equation 3 is a generalised model that determines the net economic effect of using a given health-enabling nutrient on the odds of a predefined set of event outcomes. Because of the additive nature of the model, one can easily add in additional expected health benefits and costs that are related to the health condition of interest. However, for the purposes of this study, only the cost savings potential due to the hypothesised relationship between phytosterol use and LDL cholesterol reduction was assessed.

As stated previously, the purchase and utilisation of phytosterols is required to capture these potential cost savings from avoided CVD-attributed medical events. However, the cost of phytosterols, like other healthcare costs, will vary by country, the sales channel, the supplier, and other variables. Consequently, the cost of phytosterols will vary to reflect these economic realities. One way to control for this variance is to adjust observed market prices by the purchasing power of each country's citizens. [15]

However, it is difficult to find reliable information on the cost of phytosterol food supplements in Europe since the majority of food supplement products in the market contain a mix of various components and food ingredients and thus it is not feasible to find the cost of phytosterols as single ingredient. For the few single component products that were found, the cost per 1,000 mg ranged from € 0.24 to € 0.47 (average € 0.33; median € 0.28) based on a review conducted by the authors of this case study. Consequently, a 1.7 gram daily regimen of a phytosterol food supplement would cost on average € 0.56 daily or a median price of € 0.48 per day. Furthermore, phytosterols from margarine, one of the main carriers for phytosterols in food, is typically priced at € 1.59 to € 2.99 per 250 gram pack. Each 250 gram pack delivers approximately 15 grams of phytosterols. Thus, the expected consumer price of phytosterols from margarine is € 0.10 to € 0.18 per gram or € 0.16 to € 0.30 per 1.7 grams. Assuming that the consumer would replace a standard margarine with a margarine enriched with phytosterols, the additional cost per day would be between € 0.08 and € 0.13 per gram per day.

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15 [10] The World Bank. http://data.worldbank.org/indicator/PA.NUS.PPPC.RF. According to the World Bank, purchasing power parity (PPP) is a factor that adjusts a given country's domestic value of a Euro required to buy a given product to a baseline country's value of a Euro. For the purposes of this analysis, the purchasing power of a Euro in Belgium was assumed to be 100 versus the other European Union countries. It should be noted that PPP merely reflects the relative value of a Euro across two and more countries and does not establish the baseline value of a Euro.

Thus, for the purposes of this case study, a average daily cost of 1.7 grams of phytosterols was set at € 0.56 per day, or approximately € 204.54 per year. This median price was then weighted by each country's PPP ratio from the World Bank in order to best represent the expected variance in phytosterol prices observed in other EU markets not included in the subset of countries listed above [10]. Accordingly, the cost of phytosterol utilisation required to realise the expected benefits by the total target population of all adults age 55 and older with severe hypercholesterolemia (>6.2 mmol/L) at risk of experiencing a CVD-attributed medical events per year, ***C***, is expected to be € 1.213 billion per year. Table 7 shows the expected daily and annual costs of using phytosterol daily in the EU after ensuring purchasing power parity across all EU countries and the total potential cost of phytosterols per country.

The average cost of using phytosterols at recommended daily intake levels is approximately €0.56 per day, or approximately €204.54 per year.

Table 7
Economic Benefits from Phytosterols Food Supplement Use: Expected Consumer Price per Phytosterols Supplements per Day per EU Country, adjusted for Purchasing Power Parity, 2015/2016

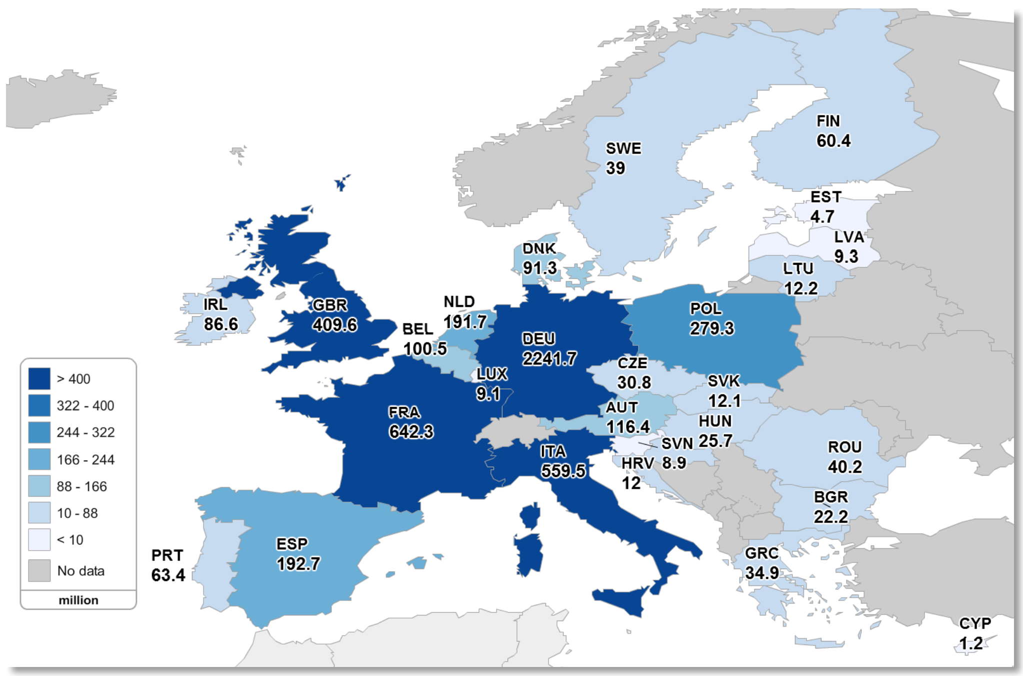
Country	d/day: Average Daily Cost of 1.7 grams of a Phytosterol Food Supplement, € /day	d: Average Annual Cost of Phytosterols Food Supplement, € /year	PPP: Purchasing Power Parity Weights, 2014/2015 (Belgium € = 100)
Austria	€ 0.55	€ 202.49	98
Belgium	€ 0.57	€ 206.59	100
Bulgaria	€ 0.26	€ 95.02	45
Croatia	€ 0.31	€ 113.61	55
Cyprus	€ 0.46	€ 169.40	82
Czech Republic	€ 0.33	€ 120.68	55
Denmark	€ 0.72	€ 261.81	127
Estonia	€ 0.40	€ 145.22	64
Finland	€ 0.63	€ 231.13	109
France	€ 0.56	€ 204.54	91
Germany	€ 0.53	€ 192.27	91
Greece	€ 0.44	€ 159.54	73
Hungary	€ 0.29	€ 106.36	55
Ireland	€ 0.61	€ 222.95	100
Italy	€ 0.53	€ 192.27	91
Latvia	€ 0.36	€ 132.21	64
Lithuania	€ 0.31	€ 113.61	55
Luxembourg	€ 0.63	€ 229.08	109
Malta	€ 0.41	€ 150.80	73
Netherlands	€ 0.57	€ 208.63	100
Portugal	€ 0.29	€ 104.32	82
Poland	€ 0.41	€ 149.31	55
Romania	€ 0.26	€ 95.02	45
Slovakia	€ 0.35	€ 128.86	64
Slovenia	€ 0.42	€ 153.41	73
Spain	€ 0.47	€ 171.81	82
Sweden	€ 0.61	€ 222.95	118
United Kingdom	€ 0.68	€ 247.49	120
Median EU	**€ 0.56**	**€ 204.54**	--

Source: Frost & Sullivan analysis

The daily use of 1,700 mg of supplement by all Europeans age 55 and older with high LDL-cholesterol and potentially yields €5.30 billion in avoidable health care costs per year.

Given the annual average cost per person for a CVD-related event (€ 34,637) and the 170,542 possible of avoidable CVD-attributed events if the entire target population of users per year, the total potential avoidable hospital utilisation cost for all EU adults over the age of 55 with hypercholesterolemia given the use of phytosterols would average €5.30 billion per year to health care cost payers. Cyprus has the lowest potential savings (€1.2 million per year) and Germany had the highest potential savings of €2.2 billion in avoided hospital event costs per year. Overall, the five largest EU countries (France, Germany, Italy, Spain, and the UK) can expect potential cost savings in excess of €160 million per year. Table 7 and Chart 3 show the total healthcare costs savings that are possible from avoided CVD-attributed hospital events by EU country.

Chart 3
Phytosterols Summary Economic Results, Total Potential Health Care Cost Savings, € million, Annualised Average, EU, 2015-2020
Total EU: €5.30 billion



Source: Frost & Sullivan analysis.

Table 7
Economic Benefits from Phytosterols Food Supplement Use: Avoided Healthcare Costs by EU Country, 2015

Country	A: Annualised Average # of Avoided CVD-attributed Events from use of Phytosterols	h: Adjusted Average Annual Cost of CVD-attributed Hospital Event, € /event	S = A*h: Expected 1 Year Total Avoided Cost of CVD-attributed Events	C: Total Cost of Phytosterols per year	B = S - C: Net Benefit
Austria	4,206	€ 28,248	€ 116,421,563	€ 19,623,323	€ 96,798,240
Belgium	3,953	€ 25,422	€ 100,489,547	€ 32,559,074	€ 67,930,473
Bulgaria	1,648	€ 29,684	€ 22,229,744	€ 4,590,059	€ 17,639,685
Croatia	717	€ 30,555	€ 11,955,933	€ 3,175,339	€ 8,780,593
Cyprus	27	€ 51,613	€ 1,160,027	€ 1,154,366	€ 5,661
Czech Republic	2,143	€ 26,371	€ 30,824,293	€ 9,109,321	€ 21,714,972
Denmark	2,288	€ 31,362	€ 91,314,254	€ 29,032,906	€ 62,281,348
Estonia	430	€ 17,068	€ 4,674,021	€ 2,028,765	€ 2,645,256
Finland	1,833	€ 30,208	€ 60,404,936	€ 16,161,808	€ 44,243,128
France	17,218	€ 41,034	€ 642,296,218	€ 173,800,271	€ 468,495,946
Germany	66,085	€ 37,313	€ 2,241,662,933	€ 323,925,959	€ 1,917,736,974
Greece	1,262	€ 38,041	€ 34,915,609	€ 9,265,860	€ 25,649,748
Hungary	3,554	€ 13,244	€ 25,676,191	€ 10,588,597	€ 15,087,594
Ireland	1,496	€ 57,865	€ 86,575,611	€ 11,040,681	€ 75,534,930
Italy	17,288	€ 35,597	€ 559,465,405	€ 157,289,923	€ 402,175,482
Latvia	609	€ 24,040	€ 9,312,405	€ 2,701,848	€ 6,610,557
Lithuania	1,896	€ 11,777	€ 12,181,892	€ 2,955,942	€ 9,225,949
Luxembourg	292	€ 28,677	€ 9,120,676	€ 2,100,946	€ 7,019,730
Malta	95	€ 38,436	€ 2,656,492	€ 749,730	€ 1,906,762
Netherlands	3,861	€ 49,663	€ 191,728,960	€ 42,802,905	€ 148,926,055
Portugal	2,292	€ 33,814	€ 63,403,958	€ 13,467,077	€ 49,936,881
Poland	12,247	€ 41,814	€ 279,323,560	€ 36,776,514	€ 242,547,045
Romania	2,979	€ 29,684	€ 40,201,768	€ 8,299,931	€ 31,901,837
Slovakia	1,401	€ 13,609	€ 12,131,024	€ 4,623,316	€ 7,507,708
Slovenia	536	€ 22,916	€ 8,937,330	€ 3,256,172	€ 5,681,158
Spain	5,698	€ 41,339	€ 192,721,220	€ 63,399,319	€ 129,321,901
Sweden	1,408	€ 23,410	€ 38,966,407	€ 14,615,794	€ 24,350,613
United Kingdom	13,079	€ 26,099	€ 409,608,977	€ 214,748,639	€ 194,860,338
Total EU	**170,542**	**€ 34,637**	**€5,300,360,955**	**€ 1,213,844,388**	**€ 4,086,516,567**

Source: Frost & Sullivan analysis

Net health care cost savings from avoided CHD-attributed events can is as much as €1.65 billion per year, or €3.74/€1 spent on a phytosterol supplement regimen per year.

Table 8
Avoided Healthcare Costs from Phytosterol Supplement Use: Avoided Costs of Hospital Events and Benefits per Target User by EU Country, 2015

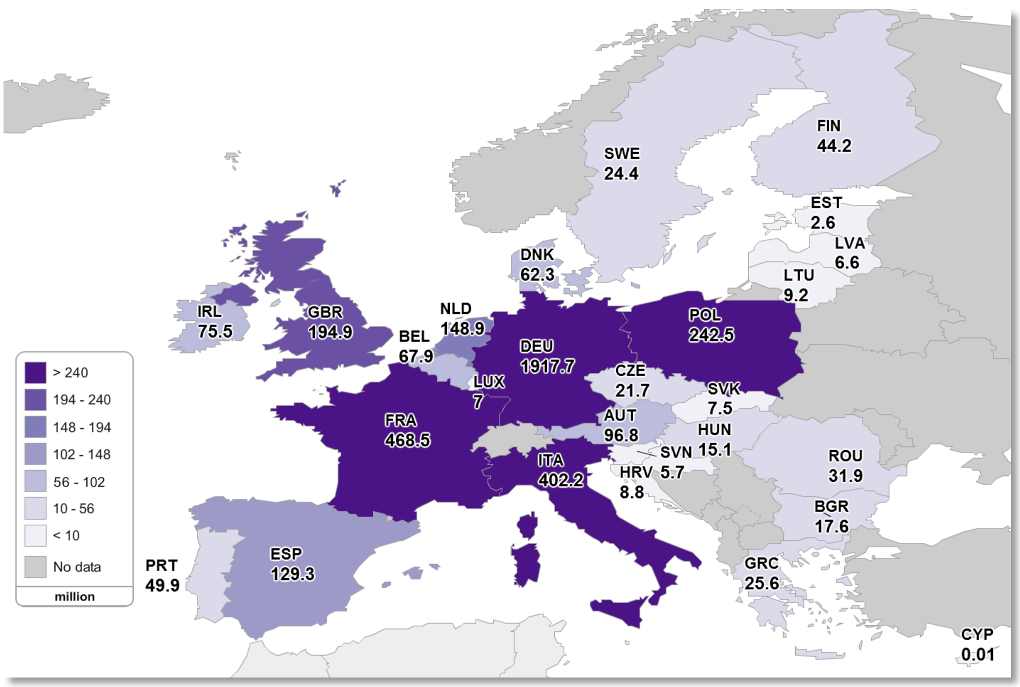
Country	B: Expected Net Benefits from Avoided Cost of CVD-attributed Events	S/Pop: Total Benefit per User (Adjusted Avoided CVD-attributed Healthcare Costs per person per EU country), €/person, Europe, Annualised Average, 2016-2020	S/C: Benefit Cost Ratio (€ Avoided Costs and Gains per € 1 spent on Phytosterols Food Supplements)
Austria	€ 96,798,240	€ 233.06	€ 5.93
Belgium	€ 67,930,473	€ 137.72	€ 3.09
Bulgaria	€ 17,639,685	€ 65.34	€ 4.84
Croatia	€ 8,780,593	€ 61.17	€ 3.77
Cyprus	€ 5,661	€ 30.13	€ 1.00
Czech Republic	€ 21,714,972	€ 62.48	€ 3.38
Denmark	€ 62,281,348	€ 209.98	€ 3.15
Estonia	€ 2,645,256	€ 61.90	€ 2.30
Finland	€ 44,243,128	€ 170.18	€ 3.74
France	€ 468,495,946	€ 155.71	€ 3.70
Germany	€ 1,917,736,974	€ 327.31	€ 6.92
Greece	€ 25,649,748	€ 76.95	€ 3.77
Hungary	€ 15,087,594	€ 46.17	€ 2.42
Ireland	€ 75,534,930	€ 379.37	€ 7.84
Italy	€ 402,175,482	€ 137.46	€ 3.56
Latvia	€ 6,610,557	€ 82.02	€ 3.45
Lithuania	€ 9,225,949	€ 79.60	€ 4.12
Luxembourg	€ 7,019,730	€ 254.59	€ 4.34
Malta	€ 1,906,762	€ 102.59	€ 3.54
Netherlands	€ 148,926,055	€ 187.84	€ 4.48
Portugal	€ 49,936,881	€ 139.44	€ 4.71
Poland	€ 242,547,045	€ 117.40	€ 7.60
Romania	€ 31,901,837	€ 55.69	€ 4.84
Slovakia	€ 7,507,708	€ 53.08	€ 2.62
Slovenia	€ 5,681,158	€ 76.21	€ 2.74
Spain	€ 129,321,901	€ 85.65	€ 3.04
Sweden	€ 24,350,613	€ 87.97	€ 2.67
United Kingdom	€ 194,860,338	€ 102.44	€ 1.91
Total EU	**€ 4,086,516,567**	**€ 170.46**	**€ 4.37**

Source: Frost & Sullivan analysis

As shown in Tables 7 and 8, the total net benefit, ***B***, for the entire EU target population all adults age 55 and older with severe hypercholesterolemia is **€ 4.09 billion** per year. This means that for every € 1.00 spent on a phytosterol daily regimen, there would be a certainty equivalent return to the primary payers of healthcare costs, which include governments and insurance companies, of **€ 4.37** to society in the form of avoided healthcare expenditures attributed to CVD. In fact, all 28 EU countries have benefit cost ratios greater than € 1.00 which is an indication of phytosterol's cost effectiveness. The greatest net benefits are found in Germany, where an expected annualised net benefit from avoided CVD-attributed healthcare costs is € 1.92 billion per year. Germany is followed by France and Italy with € 468.5 million and € 402.2 million in per year in total net benefits, respectively. Chart 4 shows the net benefits from avoided CVD-attributed events through the use of phytosterol supplements and Chart 5 displays the monetary gains in health care cost savings per € 1.00 spent on a phytosterol regimen. Tables 7 and 8 describe the detailed results of the economic analysis by EU country.

The total net benefit, B, for the entire EU target population of adults age 55 and older with severe hyper-cholesterolemia is € 4.09 billion per year.

Chart 4
Phytosterols Summary Economic Results, Total Net Benefits (Potential Health Care Cost Savings Excluding Expected Cost of Supplement), € million, Annualised Average, EU, 2015-2020
Total EU: €4.09 billion

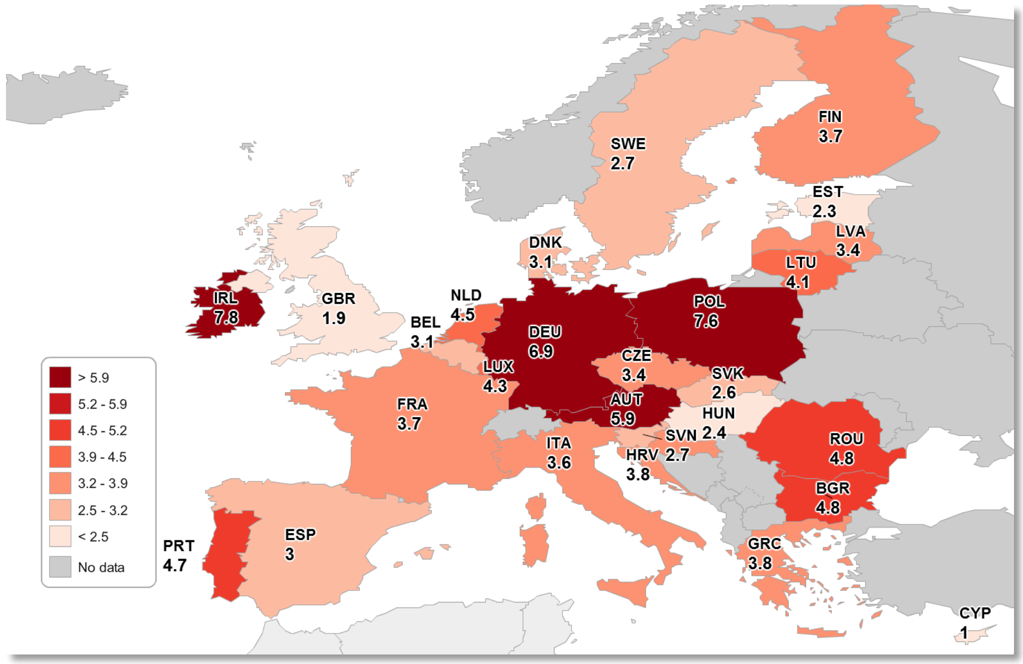


Source: Frost & Sullivan analysis.

For every € 1.00 spent on a phytosterol daily regimen, there would be a certainty equivalent return to the primary payers of healthcare costs of € 4.37 in the form of avoided healthcare expenditures attributed to CVD.

Chart 5
Phytosterols Summary Economic Results, Expected Cost Effectiveness or the expected € Gains in Health Care Cost Savings per € 1.00 Spent on a Phytosterol Regimen, EU, 2015-2020

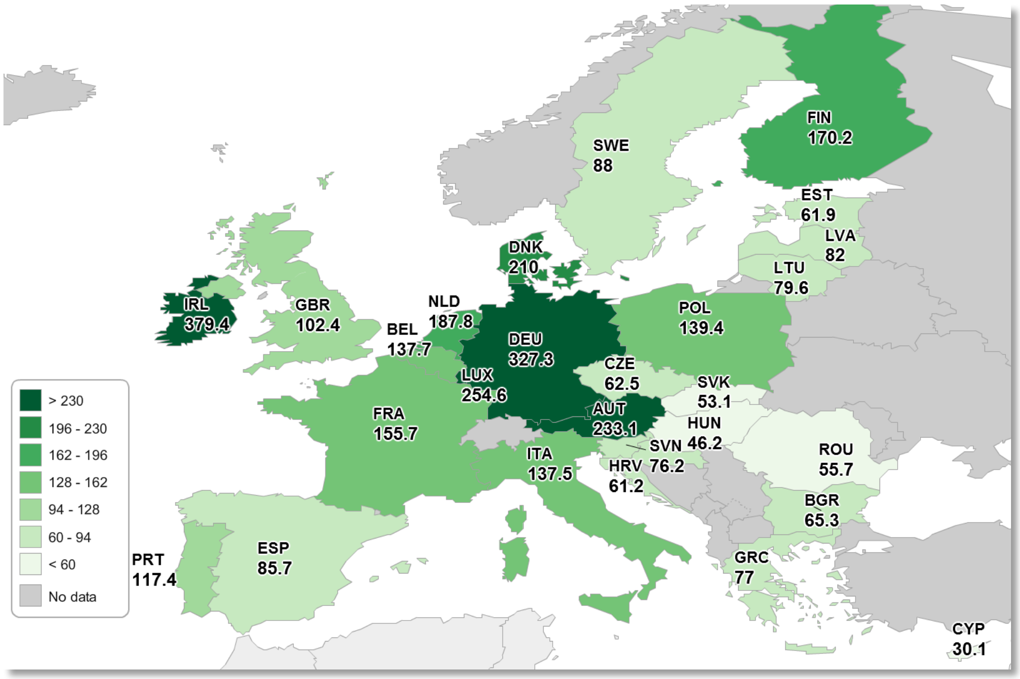
Total EU: €4.37/ €1 Spent on Phytosterol Supplement



Source: Frost & Sullivan analysis.

Chart 6 shows per EU country statistics on the total CVD health economic benefits per potential user of a phytosterols regimen per day. As shown in the chart, the benefits per phytosterol user from the target population highly varies and is dependent on relative healthcare costs in each country and the risk of that given individual experiencing a CVD-attributed event. Knowing per user benefits is a more useful measure of potential benefits because this statistic can be paired with consumer research insights in order to calculate the portion of the target population who are not current users of phytosterols and who are yet to realise the potential benefits of using phytosterol. Overall, the benefits per potential user (all adults age 55 and older with severe hypercholesterolemia) are expected to be € 170.46 per user. The greatest benefits per user was found to be in Ireland (€379 per target user per year) which is likely due to this country having a relatively high cost of care for CVD, after adjusting for purchasing power parity. On the other hand, the net benefits per person in Cyprus and Hungary, have small, yet still positive, benefits per person due to lower healthcare cost burden these countries have in general even after adjusting for purchasing power parity. It should be noted that this does not mean that these countries would not benefit from using phytosterols daily, because these countries are still avoiding a significant number of CVD-attributed events that are directly attributed to lower productivity, higher healthcare costs, and a lower quality of life.

Chart 6
Phytosterols Summary Economic Results, Total Potential Health Care Cost Savings per Capita, €/Target User, Annualised Average, EU, 2015-2020
Total EU: €170.46/Target User



Source: Frost & Sullivan analysis.

The benefits per potential user (all adults age 55 and older with severe hyper-cholesterolemia) are expected to be €170.46 per user for the EU as a whole.

The potential cost saving derived from the use of phytosterol food supplements is expected to be significant because of the direct link to lowering LDL cholesterol levels.

Concluding Remarks

Phytosterols could confer significant potential healthcare cost savings for all EU adults over the age of 55 with hypercholesterolemia. As shown above, there has been a significant amount of research exploring the benefits of using phytosterols and there is an indication that phytosterols produce a likely positive impact on CVD risk reduction through the reduction of baseline LDL cholesterol levels of users. Furthermore, the potential benefits of using phytosterols increases with increases in the severity of hypercholesterolemia. The potential cost saving derived from the use of phytosterols is expected to be significant because of the direct link to lowering LDL cholesterol levels. It is because of this direct link that the postulation was made that there would be consequential impact on reducing the risk of experiencing a CVD event.

Regarding the potential limitations of this case study, the potential healthcare cost saving calculations reported in this study only include the direct and indirect expenditures most likely to be associated with the use of phytosterols. These estimates do not include a number of additional benefits that can be gained from the use of phytosterols, including additional benefits related to avoiding other potentially costly CVD-attributed events such as reduced stress and worry experienced by patients and the families of patients. It also does not include productivity gains that can be derived from helping otherwise healthy people avoid CVD-attributed medical events, which directly impacts additional benefits to the state in the form of tax revenue. However, the economic model utilised for this analysis is a generalised model that determines the economic effect of using phytosterols on the chance a CVD-attributed event outcome, which is directly relevant to the social cost of healthcare.

In addition, the current case study does not follow individual people over time due to data availability limitations. This economic model currently treats all of the people in the target population per EU country as a homogeneous set of people, including the expected risk of experiencing a CVD-attributed disease-attributed event. Thus, total social benefits are measured. Actual benefits realised per individual user will be a function of the specific CVD risk they face as indicated by their risk biomarker levels.

The case study also makes the inference that in the phytosterol utilisation scenario all adults over the age of 55 with CVD use phytosterols from a base of zero usage among this population segment. In other words, the calculated net savings is actually the total potential net savings. However, because it is likely that a percentage of target population are already regular users of phytosterols, this portion of the target population is already realizing phytosterol's risk-reducing benefits. According to the 2012 Council for Responsible Nutrition Consumer Survey on Dietary Supplements, less than 1% of U.S. adults over the age of 55 are regular users of phytosterols food supplements which imply that the target population highly underutilises phytosterols in general [24]. It is expected that the EU as a whole reflects similar phytosterol supplement consumption patterns to the U.S, though the use of phytosterols-fortified foods is likely greater in the EU compared to the U.S. Thus, this is the key reason why benefits per user were calculated so that once consumption trends per user per EU country are determined through future research, then calculation of total potential benefits yet to be realised per country can be easily determined.

In conclusion, this case study on the potential benefits of using phytosterols illustrates that there are significant health care cost savings likely to be realised. However, this can only be achieved through a concerted effort to identify high CVD-risk populations, such as those people with severe hypercholesterolemia, and encourage them to use phytosterols as a means to help minimise the risk they face. There are many ways to identify and motivate people at risk to use effective food supplements, including the use of innovative technologies that are able to identify high-risk populations before they experience costly acute treatment events or the use of incentives for consumers, health care professionals, and other key stakeholders to address the antecedents of disease. Once these innovative technologies and best practices are fully adopted and applied by the key stakeholders in the health care system in the European Union, then a smarter approach that utilises certain food supplements that have been shown scientifically to reduce the risk of experiencing a costly CVD event at controlling potential health care costs can be applied to truly maximize the total potential social benefit of avoided cases of CVD.

Significant health care cost savings can to be realized through a concerted effort to identify high CVD risk populations and encourage them to use phytosterol food supplements as a means to help minimise the risk they face.

References

[1] World Health Organization. Regional Office for Europe. European hospital morbidity database [1] Hypercholesterolemia. (2016) Genetics Home Reference. U.S. National Library of Medicine. Retrieved at https://ghr.nlm.nih.gov/condition/hypercholesterolemia.

[2] Blood Cholesterol (HDL, LDL, & Triglycerides) (2016). ExRx.net. Retrieved September 2016.

[3] World Health Organization. Global Health Observatory (GHO) data. Retrived in September 2016 at http://www.who.int/gho/ncd/risk_factors/cholesterol_prevalence/en/

[4] Nichols, Melanie, Nick Townsend, Peter Scarborough, and Mike Rayner. European Cardiovascular Disease Statistics 2012. European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis, 2012.

[5] World Health Organisation Regional Office for Europe. European Hospital Morbidity Database. 2015. http://data.euro.who.int/hmdb/ (accessed March 2015).

[6] Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;Aug 27. Retrieved at http://eurheartj.oxfordjournals.org/content/early/2016/08/26/eurheartj.ehw272

[7] Shanahan. C. (2016) The Healthcare Cost Savings of Omega-3 Food Supplements in the European Union. Frost & Sullivan. 2016. Available at http://www.foodsupplementseurope.org/sites/0023/uploads/content/hccs-omega-3/hccs-omega-3-report.pdf

[8] Eurostat. European Commission (http://ec.europa.eu/eurostat/data/database)

[9] Nichols, Melanie, Nick Townsend, Peter Scarborough, and Mike Rayner. "Cardiovascular disease in Europe 2014: epidemiological update." (European Heart Journal) 35, no. 42 (2014).

[10] The World Bank. Data. 2015. http://data.worldbank.org/indicator/SP.POP.TOTL (accessed March 2015).

[11] IMPROVE-it study. (2016) Improved Reduction of Outcomes: Vytorin Efficacy International Trial. Retrived at http://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469669.pdf)

[12] Cannon et. al. (2016) Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015; 372:2387-2397June 18, 2015. Retrived at http://www.nejm.org/doi/full/10.1056/NEJMoa1410489#t=article.

[13] European Atherosclerosis Society (2015) Commentary on Phytosterol-added Foods. Focus on lifestyle: EAS Consensus Panel Position Statement on Phytosterol-added Foods. Retrieved at https://www.eas-society.org/?phytosterol_comment

[14] Delahoy PJ, Magliano DJ, Webb K, Grobler M, Liew D: The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: An updated meta-analysis. Clinical Therapeutics 2009, 31(2):236-244

[15] Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R: Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. Mayo Clin Proc. 2003, 78(8):965-78.

[16] Gould AL1, Davies GM, Alemao E, Yin DD, Cook JR: Cholesterol reduction yields clinical benefits: meta-analysis including recent trials. Clin Ther. 2007 May;29(5):778-94.

[17] Racette, S. B., Spearie, C. A., Phillips, K. M., Lin, X., Ma, L., & Ostlund, R. E. (2009). Phytosterol-deficient and high-phytosterol diets developed for controlled feeding studies. Journal of the American Dietetic Association, 109(12), 2043–2051.

[18] Ostlund, R. (2002). Phytosterols in Human Nutrition. Annual Review of Nutrition , 22: 533-549.

[19] Gylling, H. et al. (2014) Plant sterols and plant stanols in the management of dyslipidaemia and prevention of cardiovascular disease. Atherosclerosis. 2014 Feb;232(2):346-60. Retrieved at http://linkinghub.elsevier.com/retrieve/pii/S0021-9150(13)00694-1

[20] EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of health claims related to plant sterols and plant stanols and maintenance of normal blood cholesterol concentrations (ID 549, 550, 567, 713, 1234, 1235, 1466, 1634, 1984, 2909, 3140), and maintenance of normal prostate size and normal urination (ID 714, 1467, 1635) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. EFSA Journal 2010;8(10):1813. [22 pp.].

[21] The European Commission. (2014) Commission Regulation (EU) No 686/2014 of 20 June 2014 amending Regulations (EC) No 983/2009 and (EU) No 384/2010 as regards the conditions of use of certain health claims related to the lowering effect of plant sterols and plant stanols on blood LDL cholesterol Text with EEA relevance. Retrieved here http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2014.182.01.0027.01.ENG

[22] Phillips, C.; Belsey, J.; Shindler, J. (2002) Flora pro.activ: a clinical and financial impact analysis. Journal of Drug Assessment. Vol. 3 No. 3 pp. 179-194

[23] A. Gerber1, T. Evers, H. Haverkamp, and K. W. Lauterbach. (2006) Cost-benefit analysis of a plant sterol containing low-fat margarine for cholesterol reduction. Eur J Health Econ 2006 • 7:247–254

[24] Shanahan, C. and de Lorimier, R. (2013). Smart Prevention—Health Care Cost Savings Resulting from the Targeted Use of Dietary Supplement. An Economic Case for Promoting Increased Intake of Key Dietary Complementary medicines as a Means to Combat Unsustainable Health Care Cost Growth in the United State. Frost & Sullivan. http://www.frost.com/sublib/display-market-insight.do?id=285115104

[25] Ras RT, Geleijnse JM, Trautwein EA. (2014) LDL cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. Br J Nutr. 2014 Jul 28;112(2):214-9.

[26] Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13;110(2):227-39

[27] European Atherosclerosis Society (2015) Commentary on Phytosterol-added Foods. Focus on lifestyle: EAS Consensus Panel Position Statement on Phytosterol-added Foods. Retrieved in September 2016 at https://www.eas-society.org/?phytosterol_comment

Appendix I: Risk and Number Needed to Treat Calculations

According to Grundy et al. (2004) the relationship between RR_x and LDL concentration is non-linear such that as RR_x increases by a certain percentage for every unit increase in LDL cholesterol [26]. This relationship can be represented with the following log-linear model:

1. $$log\, RR_x = \alpha + \beta x$$

The slope β represents the rate at which CVD risk increases per unit increase in LDL cholesterol baseline level. Slope parameter β can be calculated from these results by taking the difference in relative risks for LDL cholesterol *x-1* and *x,* or:

2. $$log\, RR_{x-1} - log\, RR_x = \alpha + \beta(x-1) - (\alpha + \beta x)$$

Solving for β yields the following identity:

3. $$log \frac{RR_{x-1}}{RR_x} = -\beta$$

This equation can be generalised to calculate the change in the relative risk of experiencing a CVD event at LDL cholesterol level *x* given a change of LDL cholesterol levels by any amount as shown below:

4. $$log\, RR_{x-\delta} - log\, RR_x = log\left(\frac{RR_{x-\delta}}{RR_x}\right) = \alpha + \beta(x-\delta) - (\alpha + \beta x)$$

where δ is the expected change in LDL cholesterol given the use of a LDL cholesterol lowering regimen, like phytosterols, observed in the scientific literature. In other words, we can say that δ is the pooled treatment effect of phytosterol supplement use on LDL cholesterol.

This equation can be simplified to the following:

5. $$log\left(\frac{RR_{x-\delta}}{RR_x}\right) = -\delta * \beta$$

Plugging in for -β yields:

6. $$log\left(\frac{RR_{x-\delta}}{RR_x}\right) = \delta * log\left(\frac{RR_{x-1}}{RR_x}\right)$$

Taking the anti-log of both sides of the equation yields:

7. $$\frac{RR_{x-\delta}}{RR_x} = \left(\frac{RR_{x-1}}{RR_x}\right)^{\delta}$$

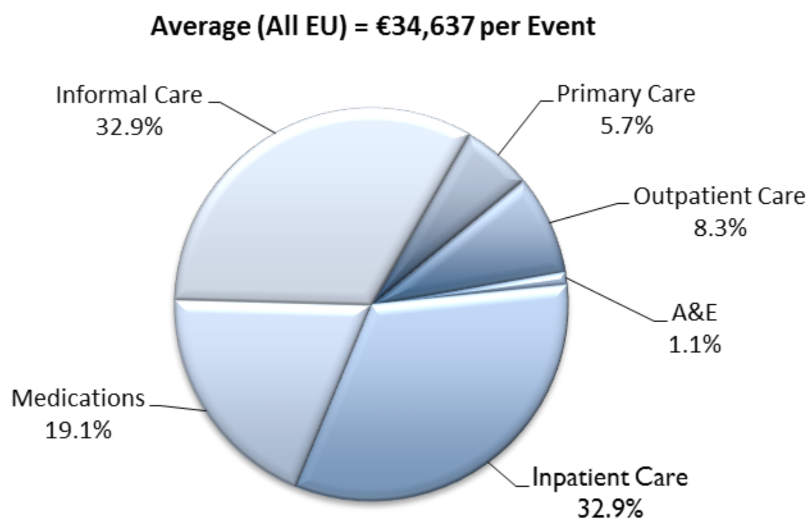
The term in parentheses is the relative risk reduction in a CVD event given a 1 unit reduction in LDL cholesterol. The term on the right side of the equal sign can be included in a general absolute risk reduction equation as shown below which in turn can be used to determine the number of possible avoided events for a predetermined target population that could be realised from use of a phytosterol supplement:

8. $$N = Risk_x \left(1 - \left(\frac{RR_{x-1}}{RR_x}\right)^{\delta}\right)$$

Appendix II: The Cost of Cardiovascular Disease

The PPP-adjusted average cost of a CVD-attributed hospital event in the EU will be € 34,637 per event[16]. The average cost of each CVD-attributed event is calculated by taking total expenditure over the next 5 years and dividing it by the cumulative number of events, and then adjusting each country's expected cost by its PPP. The cost of inpatient care, which is the expenditure for care of patients who requires hospital admission at the beginning of the CVD-attributed event, and post-treatment informal costs such as home nurses, medical equipment for home use and lost productivity which is typically spent over several months or years after the initial event are nearly equal in share of cost burden at 32.9% each. The cost of medications for managing CVD makes up an additional 19.1% of the financial burden of CVD. The remaining services contributing to CVD-attributed healthcare costs make up a combined 15.1% of the cost burden include primary care (5.7%), outpatient care (8.3%) and ambulance and emergency (A&E) (1.1%).

Appendix Chart 1
Total Burden of Cardiovascular Disease: CVD-attributed Event Costs by Service Type, European Union, 2015[17][18]



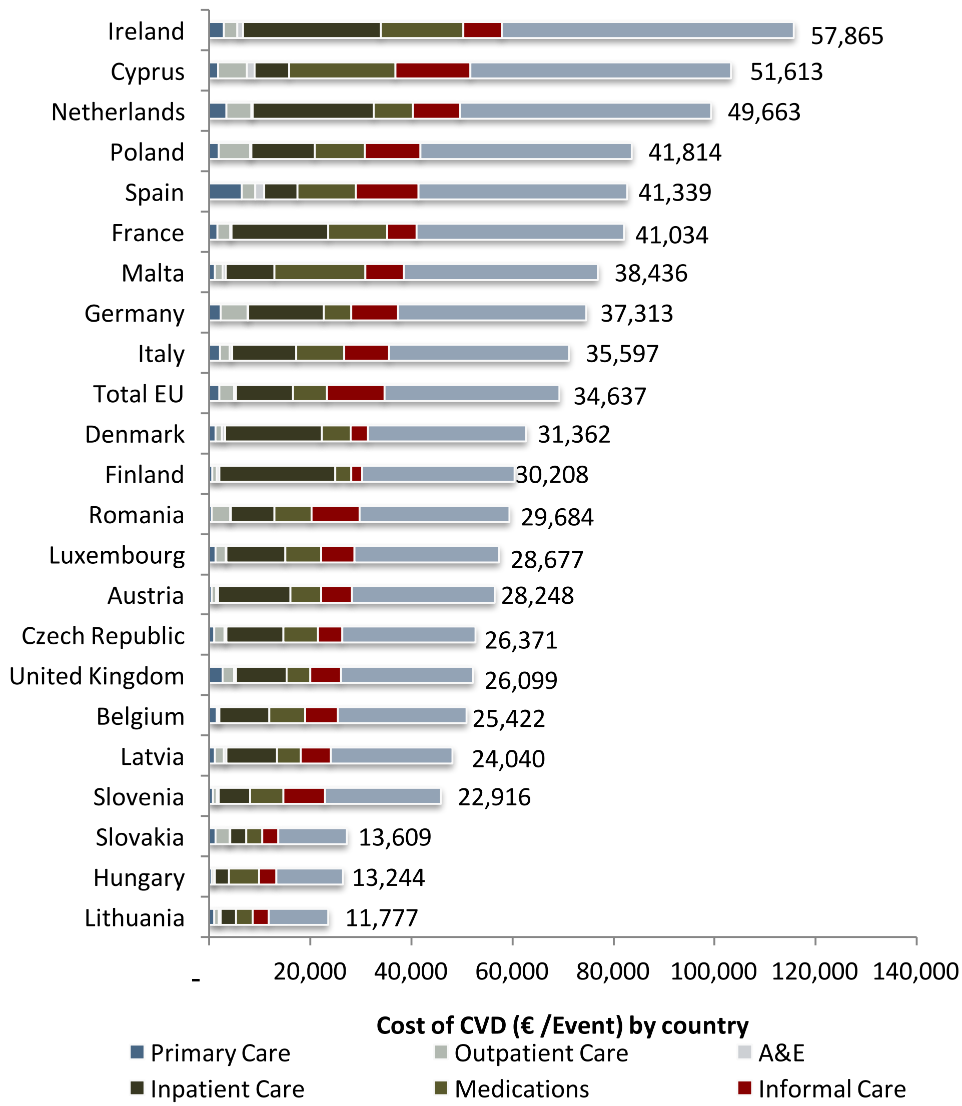
16 Source: European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis, Frost & Sullivan. The average cost of each CVD-attributed event is calculated by taking total expenditure over the next 5 years and dividing it by the cumulative number of events. This event cost was taken because some events and its residual post treatment disease management costs may stretch beyond one year for a given patient.

17 Adjusted for purchasing power parity (PPP). PPP ratios are provided by the World Bank and are reported in Table 8 of this report or http://data.worldbank.org/indicator/PA.NUS.PPPC.RF.

18 Note: A&E is ambulance and emergency services. Inpatient care is the expenditure for care of patients who requires hospital admission at the beginning of the CVD-attributed event. Informal Care includes post-treatment informal costs such as home nurses, medical equipment for home use and lost productivity which is typically spent over several months or years after the initial event. Outpatient care includes costs related to medical care provided on an outpatient basis, including diagnosis, observation, consultation, treatment, intervention, and rehabilitation services. Primary care is the day-to-day healthcare given by a health care provider. Source: European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis, Frost & Sullivan analysis

Appendix Chart 2

Total Burden of Cardiovascular Disease: CVD-attributed Event Costs by Service Type: Ranked by Total Hospital Event Costs, Selected EU Countries, 2015[19]



Source: European Heart Network, Brussels, European Society of Cardiology, Sophia Antipolis, Frost & Sullivan analysis

19 Adjusted for purchasing power parity (PPP). PPP ratios are provided by the World Bank and are reported in Table 8 of this report or http://data.worldbank.org/indicator/PA.NUS.PPPC.RF.

Appendix III: List of Abbreviations

A	Number of possible avoided events (A) if everybody in a specified target population used phytosterol
B	total potential net economic benefits yet to be realised from use of a 1,000 mg phytosterol
S/Pop	Benefit per User
BP	Blood Pressure
C	Total cost of a phytosterol regimen
CBA	Cost-benefit analysis
CI	Confidence interval
CHD	Coronary heart disease
CVD	Cardiovascular disease
d	The expected per person cost of phytosterol utilisation per year
EFSA	European Food Safety Authority
EU	European Union
g	gram
h	The expected cost of a CVD-attributed event
HDL	High-density lipoprotein
ICD	International Classification of Diseases
IHD	Ischemic heart disease
ISHMT	International Shortlist for Hospital Morbidity Tabulation
LDL	Low-density lipoprotein
mg	milligram
MI	myocardial infarction
mmol/L	millimole per liter
N*	Absolute risk reduction
Pop	Target Population
PPP	Purchasing Power parity
RCT	Randomised controlled trials
RRR	Relative risk reduction
S	Total potential savings from reduced hospital service utilisation following CHD-attributed hospital events that are realisable if the entire target population were to sufficiently utilise a 1,000 mg phytosterol
S/C	Benefit Cost Ratio
S/Pop	Benefit per User
U.S.	United States of America
WHO	World Health Organization

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