EU HEALTHCARE COST SAVINGS FROM FOOD SUPPLEMENTS: THE VALUE OF OMEGA-3, PHYTO-STEROLS AND BETA-GLUCANS SUPPLEMENTATION FOR REDUCING RISK FACTORS ASSOCIATED WITH CARDIOVASCULAR DISEASE

A tool for translating nutrient efficacy into consumer health value

Véronique Scordia, PhD
Christopher J. Shanahan

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https://www.foodsupplementseurope.org/

12 Hammersmith Grove
London, W6 7AP
Phone: +44 (0)20 3310 1200
myfrost@frost.com

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List of abbreviations:

ACRONYM	FULL TERM
AF	Atrial fibrillation
AHA	American Heart Association
ALA	Alpha-linolenic acid
AMI	Acute myocardial infarction
ARR	Absolute Risk Reduction
ASCVD	Atherosclerotic cardiovascular disease
ASMR	Age-standardised mortality rate
ASR	Age-standardised rate
BCR	Benefit-cost ratio
BG	Beta-Glucan (shorthand used in model tables)
BP	Blood pressure
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CAGR	Compound annual growth rate
CEE	Central and Eastern Europe
BER	Baseline event rate
CHD	Coronary heart disease
CI	Confidence interval
CTT	Cholesterol Treatment Trialists' Collaboration
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DHA	Docosahexaenoic acid
EAS	European Atherosclerosis Society
EC	European Commission
EFSA	European Food Safety Authority
EHN	European Heart Network
EPA	Eicosapentaenoic acid
ESC	European Society of Cardiology
ESH	European Society of Hypertension

ACRONYM	FULL TERM
EU	European Union
EUR	Euro (currency)
FDA	Food and Drug Administration (US)
FH	Familial hypercholesterolaemia
FSE	Food Supplements Europe
GBD	Global Burden of Disease (IHME)
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCCS	Healthcare cost saving
HDAC	Histone deacetylase
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HTG	Hypertriglyceridaemia
H&SC	Health and Social Care
ICD	International Classification of Diseases
IDL	Intermediate-density lipoprotein
IHD	Ischaemic heart disease
IHME	Institute for Health Metrics and Evaluation
IPE	Icosapent ethyl ester
JAHA	Journal of the American Heart Association
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LPS	Lipopolysaccharide
MACE	Major Adverse Cardiovascular Events
MAMP	Microbe-associated molecular patterns
MI	Myocardial infarction
MW	Molecular weight
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
NHS	National Health Service (UK)

ACRONYM	FULL TERM
NHS	National Health Service (UK)
NNT	Number needed to treat
O3AEE	Omega-3 acid ethyl esters
O3CA	Omega-3 carboxylic acid
O3I	Omega-3 Index
OHID	Office for Health Improvement and Disparities (UK)
OOP	Out-of-pocket (healthcare expenditure)
PCI	Percutaneous coronary intervention
PCOS	Polycystic ovary syndrome
PCSK9	Proprotein convertase subtilisin/kexin type 9
PICOS	Population, Intervention, Comparator, Outcomes, Study design
PM2.5	Particulate matter ≤2.5 µm diameter
PPAR-α	Peroxisome proliferator-activated receptor alpha
PPP	Purchasing power parity
PS	Phytosterols (shorthand used in model tables)
PUFA	Polyunsaturated fatty acids
RCT	Randomised controlled trial
RR	Relative risk
RRR	Relative risk reduction
SBP	Systolic blood pressure
SCFA	Short-chain fatty acids
SREBP-1	Sterol regulatory element binding protein-1
PIER	Post-intervention event rate
TG	Triglycerides
TXA2	Thromboxane A2
UK	United Kingdom
VLDL	Very low-density lipoprotein
WHO	World Health Organization

List of clinical trials abbreviations

ACRONYM	FULL TERM
ASCEND	A Study of Cardiovascular Events in Diabetes (ASCEND Study Collaborative Group, Lancet 2018;392:1036–1045)
BELT	Beta-Glucan Effects on Lipid Profile, Glycemia and inTestinal Health Study (Cicero AF et al., Nutrients 2020;12(3):686)
GISSI-P	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico, Prevenzione (GISSI-Prevenzione Investigators, Lancet 1999;354:447–455)
JELIS	Japan EPA Lipid Intervention Study (Yokoyama M et al., Lancet 2007;369:1090–1098)
OMEMI	Omega-3 Fatty Acids in Elderly Patients with Acute Myocardial Infarction (Kalstad AA et al., Circulation 2021;143:528–539)
REDUCE-IT	Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (Bhatt DL et al., N Engl J Med 2019;380:11–22)
SANTORINI	Study to Assess Contemporary Treatment Patterns in Patients with Atherosclerotic Cardiovascular Disease or Heterozygous Familial Hypercholesterolaemia at High Risk (Ray KK et al., Lancet Reg Health Eur 2023;29:100624)
SCORE2	Systematic COronary Risk Evaluation 2, the ESC-validated 10-year cardiovascular risk prediction model for apparently healthy individuals aged 40–69 in Europe (SCORE2 Working Group, Eur Heart J 2021;42:2439–2454)
STRENGTH	Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridaemia (Nicholls SJ et al., JAMA 2020;324:2268–2280)
VITAL	Vitamin D and Omega-3 Trial (Manson JE et al., N Engl J Med 2019;380:23–32)

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EXECUTIVE SUMMARY

Cardiovascular disease is the leading cause of mortality and economic burden across the EU27 and the United Kingdom. In 2025, an estimated 5.98 million new incident cardiovascular disease cases were recorded across all ages, of which approximately 5.39 million, 90%, occurred in the population aged 55 and above, generating a total societal cost of approximately €307 billion encompassing direct healthcare and social care, informal care, and productivity losses. This burden is projected to reach €399 billion by 2035, driven by demographic ageing and rising healthcare expenditure across EU member states. These figures are consistent with the ESC Atlas of Cardiovascular Disease Statistics 2025 (Timmis et al., European Heart Journal, 2026), the most recently published authoritative source on European CVD burden, which confirms CVD as the leading cause of death across ESC member countries, reporting more than 3 million CVD deaths and 68 million disability-adjusted life years attributable to CVD in 2023.

This report quantifies the economic value of cardiovascular disease prevention through three food supplement interventions, Omega-3 EPA+DHA, Phytosterols, and Beta-Glucan, across all 28 EU27+UK geographies for the period 2025 to 2035. The analysis applies a clinical pathway framework translating published meta-analytic evidence on relative risk reduction into avoidable incident MACE events, gross societal cost savings, supplementation costs, and net economic benefit at country and aggregate level. Base-case RRRs of 5% for Omega-3 at 1,000 mg/day, 7% for Phytosterols at 1,500 mg/day, and 6.4% for Beta-Glucan at 3,000 mg/day are derived from the Yan et al. (2024) meta-regression and Gould et al. (2007) / Ference et al. (2012, 2017) risk translation framework applied to LDL-C reductions documented by Demonty et al. (2009) and Llanaj et al. (2022) respectively.

At the 2025 base year, the three interventions address an eligible population of 34.60 million adults for Omega-3, those aged 55 and above with elevated fasting triglycerides, and 83.7 million for Phytosterols and Beta-Glucan, those aged 55 and above with elevated total cholesterol or familial hypercholesterolaemia. Under full eligible population coverage, the base-case interventions collectively generate an estimated 4.842 million avoidable incident MACE events per year across the EU27+UK, with gross societal cost savings totalling €279.9 billion annually, €36.6 billion for Omega-3, €127.1 billion for Phytosterols, and €116.2 billion for Beta-Glucan. At the 2025 base year, the cost per incident MACE case, derived from the total annual societal cost of CVD in each country divided by annual incident cases projected from the IHME GBD 2023 dataset, ranges from €26,019 in Bulgaria to €110,990 in Ireland, a 4.3-fold differential that drives the geographic variation in gross societal cost savings across the model. After deducting supplementation costs at current lowest observed EU retail prices, net benefit is positive across all three interventions and all 28 EU27+UK geographies: €32.5 billion for Omega-3, €113.0 billion for Phytosterols, and €92.3 billion for Beta-Glucan in 2025, a combined €237.8 billion annually. The structural driver of positive net benefit is the dominance of the total societal CVD cost per incident case over supplementation expenditure; supplement costs represent only 11% to 21% of gross societal cost savings across all three interventions, yielding a supplementation cost-to-gross-societal-savings ratio of 0.114 for Omega-3, 0.111 for Phytosterols, and 0.206 for Beta-Glucan at EU27+UK aggregate level. Over the cumulative 2025–2035 projection window, net benefit approximates €408 billion for Omega-3, €1,416 billion for Phytosterols, and €1,159 billion for Beta-Glucan, a combined €2,984 billion across the three base-case interventions.

The net benefit figures reported here are substantially larger than those presented in the prior Frost & Sullivan healthcare cost savings study for Food Supplements Europe (Shanahan, 2016), which estimated an annual net benefit of €7.3 billion for omega-3 EPA+DHA alone across the EU. Five methodological and scope differences account for this divergence.

- First, the current model applies an incidence-based rather than prevalence-based event rate framework, which is the single most consequential methodological difference and alone accounts for a substantial share of the increase.
- Second, the economic burden dataset has been updated from the EHN 2006 estimate of approximately €169 billion to the Luengo-Fernández 2023 figure of €307 billion at the 2025 base year, nearly doubling the cost-per-incident-case denominator drives gross societal cost savings**.**
- Third, the current report adopts a full societal cost perspective encompassing direct healthcare and social care costs, informal care, and productivity losses, rather than the narrower direct cost perspective applied in 2016; the H&SC-only sensitivity in Section 7.6 isolates the direct cost contribution at €15.8 billion for Omega-3, providing the closest like-for-like comparison with the 2016 figure.
- Fourth, the current report models three interventions rather than one, with Phytosterols and Beta-Glucan addressing a substantially larger eligible population of 83.7 million adults.
- Fifth, the Omega-3 eligible population has been expanded from approximately 22 million to 34.6 million, reflecting updated European epidemiological data on triglyceride prevalence in the 55-plus age group.

Taken together, these five differences are sufficient to account for the observed divergence in headline figures; the direction of the finding, that food supplementation generates net positive economic returns across all EU27+UK geographies, is consistent with the 2016 analysis.

The sensitivity analysis confirms the robustness of the positive net benefit finding across all six parameters tested. Under the low-bound RRR scenario, net benefit remains positive at €17.8 billion for Omega-3, €62.2 billion for Phytosterols, and €45.8 billion for Beta-Glucan; under the high-bound scenario it rises to €47.1 billion, €163.9 billion, and €138.8 billion respectively. At 30% population coverage, representing a realistic near-term adoption scenario, combined annual net benefit across the three base-case interventions remains €71.3 billion, confirming that the economic case is robust well below full eligible population reach. A 50% coverage sensitivity is also presented within the modelling framework and demonstrates the expected linear scaling of costs and benefits with population uptake. Under the H&SC-only cost perspective, excluding informal care and productivity losses, net benefit remains positive at €15.8 billion, €55.6 billion, and €39.8 billion respectively. A ±20% variation in supplement retail prices has a proportionally modest effect given that supplementation costs represent 11% to 21% of gross societal cost savings across the three interventions

The three base-case interventions generate between €4.85 and €9.02 in gross societal cost savings for every €1 of supplementation expenditure at the 2025 EU27+UK aggregate level, equivalent to a net return of €3.85 to €8.02 per €1 spent after deducting supplement costs. Phytosterols at 1.5g/day delivers the highest return at €9.02 per €1 spent; Beta-Glucan at 3g/day the lowest at €4.85, reflecting its higher per-user dose cost. Geographic variation is substantial, with the gross return for Omega-3 ranging from €13.0 per €1 spent in France to €4.0 in Croatia; net benefit nevertheless remains positive in every one of the 28

EU27+UK geographies across all three interventions. Even under the most conservative H&SC-only cost perspective, the floor return is €1.70 per €1 spent for Beta-Glucan and €3.80 for Omega-3, confirming that the economic case is robust to significant downward revision of the cost base.

An additional sensitivity on the ER baseline, applying a ±10% and ±20% scalar to country-level IHME incidence proportions, is presented in Table 7.6.6. The ER baseline is the parameter most subject to definitional uncertainty, given the mismatch between the I00–I99 all-cardiovascular aggregate used in the model and the narrower clinical MACE endpoint from which the intervention RRRs are derived. At −20% ER, approximately equivalent to restricting the incidence denominator to IHD-plus-stroke only, combined net benefit falls to €181.8 billion. Net benefit remains positive across all three interventions and all 28 EU27+UK geographies at every ER assumption tested. The elasticity of combined net benefit to a 10% ER change is 1.16, modestly above the 1.0 elasticity of gross societal cost savings, because supplementation costs are fixed and do not scale with the ER baseline

Geographic analysis confirms that all 28 EU27+UK markets generate positive net benefit under all scenarios. The largest absolute net benefit is concentrated in Germany, France, Italy, Spain, and the UK, reflecting their large eligible populations. The lowest supplementation cost-to-gross-societal-savings ratios, indicating the greatest efficiency of supplementation expenditure relative to gross societal cost savings generated, are observed in France, Finland, Austria, Germany, and Sweden, driven by their higher total societal CVD costs per incident case. Beta-Glucan records the highest supplementation cost-to-gross-societal-savings ratios across all geographies, reflecting its higher per-user dose cost, though net benefit remains positive in every market. Full epidemiological, economic burden, cost-savings modelling, and methodology documentation underpinning these findings is set out in Sections 7 and 8 of this report.

At the 2025 base year, the three base-case interventions collectively generate 4.842 million avoidable incident MACE events annually under full eligible population coverage, yielding combined gross societal cost savings of €279.9 billion against supplementation costs representing 11–21% of those savings. Net benefit is positive across all three base-case interventions and all 28 EU27+UK geographies, totalling €237.8 billion under 100% coverage and €71.3 billion under the 30% near-term coverage assumption.

Parameter 2025	O3 1g/day	O3 2g/day	PS 1.5g/day	PS 3g/day	BG 3g/day
Eligible population (million)	34.6	34.6	83.7	83.7	83.7
Average NNT	57.0	31.6	40.7	23.7	44.5
Avoidable MACE events/year (million)	0.644	1.159	2.193	3.759	2.005
Gross HCCS (€ billion)	36.6	65.9	127.1	217.9	116.2
Net benefit, 100% coverage (€ billion)	32.5	57.6	113	189.7	92.3
Net benefit, 30% coverage (€ billion)	9.7	17.3	33.9	56.9	27.7
Average SC/HCCS ratio	11.4%	12.6%	11.1%	12.9%	20.6%

Table ES.1: Summary of Economic Impact by Intervention and Scenario, EU27+UK, 2025

By 2035, healthcare cost inflation of 2.8% per annum outpacing supplement price growth of 2.0–2.7% widens the gap between gross societal cost savings and supplementation costs across the three base-case interventions. Avoidable events rise modestly over the projection period, driving combined gross societal cost savings to €360.8 billion at base-case doses. Net benefit grows to €308.5 billion under full coverage, an increase of approximately 30% relative to 2025, with supplementation cost-to-gross-societal-savings ratios declining as healthcare unit costs rise faster than supplement prices.

Parameter 2035	O3 1g/day	O3 2g/day	PS 1.5g/day	PS 3g/day	BG 3g/day
Eligible population (million)	34.6	34.6	83.7	83.7	83.7
Average NNT	57.0	31.6	40.7	23.7	44.5
Avoidable MACE events/year (million)	0.644	1.2	2.2	3.8	2
Gross HCCS (€ billion)	47.4	85.4	163.7	280.6	149.7
Net benefit, 100% coverage (€ billion)	42.3	75.1	146.2	245.7	120
Net benefit, 30% coverage (€ billion)	12.7	22.5	43.9	73.7	36
Supplementation cost-to-gross-societal-savings ratio	10.90%	12.10%	10.70%	12.40%	19.80%

Table ES.2: Summary of Economic Impact by Intervention and Scenario, EU27+UK, 2035

1 PROBLEM STATEMENT

Cardiovascular disease (CVD) remains the leading cause of mortality and a primary driver of healthcare expenditure across the European Union.

As the burden of Ischaemic Heart Disease (IHD) and hypertriglyceridemia continues to grow across ageing European populations, policymakers, public health authorities, and healthcare systems are confronting an urgent and increasingly well-documented challenge: how to shift from a predominantly reactive, treatment-based model of cardiovascular care toward more cost-effective, prevention-oriented strategies that intervene earlier in the disease pathway.[1,2]

This evolution is occurring against a backdrop of rising healthcare costs, demographic ageing, and mounting pressure on public health budgets. Cardiovascular disease accounts for an estimated 11% of total healthcare expenditure across EU Member States,[3] with direct costs driven by hospitalisation, revascularisation procedures, long-term pharmaceutical management, and rehabilitation, compounded by substantial indirect costs from premature mortality and productivity losses. The total annual economic burden of CVD on the EU economy has been estimated at €282 billion for the EU27, of which approximately €155 billion represents direct health and social care costs, equivalent to 11% of total EU direct health expenditure.[4] Adding an indicative UK contribution of approximately €28.5 billion,[5] adjusted to 2021 euros, yields a combined EU27+UK societal cost of approximately €307 billion, the headline figure applied throughout this report. The EU27 estimate itself has grown from €169 billion in 2003, reflecting the unrelenting financial strain on European health systems.

Within this context, nutritional interventions targeting established, modifiable cardiovascular risk factors offer a clinically validated and economically underexplored lever for population-level risk reduction. Three interventions form the evidential core of this report. Omega-3 fatty acids (EPA and DHA) reduce circulating triglyceride levels by 15–30% through a dose-dependent relationship confirmed across large meta-analytic datasets[5] and reduce systolic blood pressure by a mean of 2.6 mmHg, with greater reductions observed in hypertensive subgroups.[6] The triglyceride-lowering effect is supported by an EU-authorised health claim at a combined EPA+DHA intake of 2,000 mg/day under EU Regulation (EC) No 1924/2006; the blood pressure-lowering effect is supported by a separate EU-authorised health claim at 3,000 mg/day; and a further EU-

1. OECD. The State of Cardiovascular Health in the European Union. OECD Publishing, Paris; 2025
2. European Commission. Communication on an EU Cardiovascular Health Plan: The Safe Hearts Plan COM (2025) 1024 final. Brussels: European Commission; 16 December 2025.
3. Timmis A, Aboyans V, Vardas P, et al. European Society of Cardiology: the 2023 Atlas of cardiovascular Disease Statistics. Eur Heart J. 2024;45(38):4019–4062
4. Luengo-Fernandez R, Walli-Attaei M, Gray A, et al. Economic burden of cardiovascular diseases in the European Union: a population-based cost study. Eur Heart J. 2023;44(45):4752–4767.
5. Wang T, Zhang X, Zhou N, et al. Association between omega-3 fatty acid intake and dyslipidaemia: a continuous dose-response meta-analysis of randomized controlled trials. J Am Heart Assoc. 2023;12:e029512.

[6] Zhang X, Ritonja JA, Zhou N, Chen BE, Li X. Omega-3 polyunsaturated fatty acids intake and blood pressure: a dose-response meta-analysis of randomized controlled trials. J Am Heart Assoc. 2022;11(11):e025071

authorised claim supports the contribution of EPA+DHA to normal cardiac function at 250 mg/day. Plant sterols reduce LDL-cholesterol by 7–12% at intakes of approximately 2 g/day through competitive inhibition of intestinal cholesterol absorption, an effect confirmed across more than 40 randomised controlled trials and supported by an EU-authorised health claim under EU Regulation (EC) No 1924/2006. Beta-glucan soluble fibre reduces LDL-cholesterol by approximately 5–7% at intakes of 3 g/day through viscous gel formation in the intestinal lumen, which impairs bile acid reabsorption and accelerates cholesterol excretion, also underpinned by an EU-authorised health claim under EU Regulation (EC) No 1924/2006. All three effects map to established cardiovascular event-reduction pathways at the population level.

Despite this evidence base, the combined economic value of these three nutritional interventions at the EU population level has not been comprehensively evaluated within a unified modelling framework.

The previous Frost & Sullivan study for Food Supplements Europe[7] and the Council for Responsible Nutrition established the foundational methodology and economic framework upon which this report builds. The present analysis revisits that work, updating it with the most recent available epidemiological, demographic, and cost-of-care data for the EU27+UK, and extending its scope to incorporate plant sterols and beta-glucan alongside omega-3 EPA+DHA, drawing on the latest clinical evidence base across all three interventions.[5,6,8]

Compounding this is a well-documented treatment gap in triglyceride and blood pressure management across Europe. Mean systolic blood pressure across the EU27+UK stands at 130.5 mmHg among males, at or above the ESC/ESH Stage 1 hypertension threshold, and most of the EU Member States record mean fasting triglyceride levels at or above the 1.7 mmol/L borderline-high threshold. Hypertension affects an estimated 36.9% of adults aged 30–79 in the WHO European Region, yet only approximately 53% of hypertensive adults receive adequate treatment and fewer than 26% achieve adequate blood pressure control.[9] Despite the scale of this population-level burden, most adults with elevated triglycerides and blood pressure remain unmanaged at the levels required to reduce their cardiovascular event risk materially. This is not primarily a failure of clinical knowledge but a failure of reach, adherence, and system capacity.

Omega-3 EPA+DHA, plant sterols, and beta-glucan supplementation address this gap not by replacing pharmaceutical management or clinical intervention but by providing clinically validated, accessible, and low-cost tools that reduce risk factor burden in the large population that current care does not adequately serve. Crucially, the three interventions act through distinct and complementary mechanisms, triglyceride and blood pressure reduction, LDL-cholesterol reduction via absorption inhibition, and LDL-cholesterol reduction via bile acid sequestration, targeting different at-risk subpopulations and generating non-overlapping economic benefits that can be modelled and aggregated.

The core hypothesis of this report is as follows: if adults at elevated cardiovascular risk adopt omega-3 EPA+DHA, plant sterol, and beta-glucan supplementation at clinically supported intake levels as part of a

[7] Frost & Sullivan. Healthcare Cost Savings of Omega-3 Food Supplements in the European Union. Commissioned by Food Supplements Europe; 2016.
[8] Calder PC. The differential effects of eicosapentaenoic acid and docosahexaenoic acid on cardiovascular risk factors: an updated systematic review of randomized controlled trials. Front Nutr. 2024;11:1423228.
[9] Timmis A, Petersen SE, Van Belle E, et al. European Society of Cardiology: cardiovascular disease statistics 2025. European Heart Journal. 2026;00:1–45

varied and balanced diet and healthy lifestyle, the resulting reductions in triglycerides, blood pressure, and LDL-cholesterol could measurably reduce the incidence of cardiovascular events across the EU27 and UK, generating substantial and quantifiable savings in direct healthcare costs and productivity losses.

Building on the methodology established in the prior Frost & Sullivan healthcare cost savings study commissioned by Food Supplements Europe[7] and the Council for Responsible Nutrition, this report aims to:

1) Critically review the clinical evidence linking omega-3 EPA+DHA, plant sterol, and beta-glucan supplementation to reductions in triglycerides, blood pressure, and LDL-cholesterol, and map these effects to established cardiovascular event-reduction pathways;[5,6,8]

2) Develop robust EU27+UK population-level estimates of healthcare cost savings across three adoption scenarios, baseline, moderate, and high, using current epidemiological, demographic, and unit cost data;[1,3,4]

3) Contextualise these findings within the EU regulatory framework, positioning all three interventions within the boundaries of current EU-authorised health claim evidence and identifying the public health case for increased supplementation uptake.

By doing so, this report provides updated, scientifically grounded, and economically robust evidence to support EU policy dialogue,[2] regulatory considerations, and public health advocacy aimed at strengthening the role of preventive nutrition in reducing the burden and cost of cardiovascular disease.

2 THE BURDEN OF CARDIOVASCULAR DISEASE IN THE EU27+UK

Cardiovascular disease remains the leading cause of mortality and a principal driver of healthcare expenditure across the EU27 and the United Kingdom.

Across the combined population of approximately 520 million adults, an estimated 5.99 million new incident cardiovascular disease cases were recorded in 2023 across all ages, of which approximately 5.39 million, 90%, occurred in the population aged 55 and above, sourced from the IHME Global Burden of Disease Study 2023, the most recently published harmonised dataset available at EU27+UK geographic granularity. Projected forward to the 2025 model base year using Eurostat demographic assumptions, the 55-plus incident case count reaches approximately 5.39 million, confirming the near-stability of the annual MACE disease pipeline across the study geography over the 2023–2025 period.

The total societal cost of CVD across the EU27+UK is estimated at approximately €307 billion at the 2025 base year, encompassing direct health and social care expenditure of €167 billion (54.4% of total), informal care costs of €84 billion (27.3%), and productivity losses of €57 billion (18.5%) attributable to premature cardiovascular mortality and morbidity, derived from the Luengo-Fernández et al. (2023) economic burden dataset inflated to 2025 using country-specific healthcare expenditure growth rates. This figure is projected to reach €399 billion by 2035, driven by demographic ageing of the 55-plus population, healthcare cost inflation, and the ongoing expansion of healthcare expenditure as a share of GDP across most EU27+UK member states. These estimates are consistent with the ESC Atlas of Cardiovascular Disease Statistics 2025 (Timmis et al., European Heart Journal, 2026), which confirms CVD as the leading cause of death across ESC member countries with more than 3 million CVD deaths and 68 million disability-adjusted life years attributable to CVD in 2023, the most recent year for which complete harmonised data are available across all ESC member countries.

The burden is unevenly distributed and does not follow a simple geographic gradient. CVD prevalence in the 55-plus population ranges from 28.9% in Malta to 45.9% in France across the 28 geographies, with high-prevalence countries spanning both Western and Eastern Europe. This apparent paradox reflects a fundamental epidemiological distinction: in Western European countries high prevalence reflects a large surviving CVD population sustained by decades of effective acute care, cardiac rehabilitation, and long-term secondary prevention; in Eastern European countries comparable or higher incidence generates a different profile shaped by higher case-fatality rates, lower post-event survival, and more limited chronic disease management infrastructure. Countries with the highest CVD mortality rates, Romania, Bulgaria, Latvia, Lithuania, and Hungary, are not necessarily those with the highest prevalence, because fewer patients survive their initial cardiovascular event to enter the prevalent pool. It is the incidence pipeline, not the prevalence stock, that drives the volume of avoidable events and the economic return to preventive supplementation modelled in this report.

The economic burden mirrors this geographic complexity. Direct H&SC costs per incident MACE case range from approximately €7,964 in Latvia to €56,638 in Ireland, a 7.1-fold differential that reflects differences in hospital tariff structures, procedure volumes, rehabilitation intensity, and healthcare system unit costs. Eastern European countries record both the highest relative CVD burden and the lowest cost per incident case, while high-income Western European markets record lower relative disease burden but substantially

higher per-case expenditure. It is the interaction of these two dimensions, disease incidence and healthcare unit cost, that determines the economic return to preventive supplementation in each geography, with the largest absolute net benefit concentrated in populous Western European markets and the most favourable supplementation cost-to-HCCS ratios observed in higher-income countries with elevated incident case costs.

The Appendix to this report provides extensive analytical depth on every dimension of the CVD burden summarised here. Section 8.1 documents the full epidemiological analysis of CVD, stroke, and ischaemic heart disease prevalence and incidence across all 28 EU27+UK geographies, disaggregated by sex, age group, and regional cluster, alongside the cardiometabolic and behavioural risk factor landscape, screening and treatment gap analysis, mortality and morbidity outcomes, economic burden, and the composite cardiovascular risk index used to stratify the study geography. Section 8.5 sets out the full CVD cost estimation and projection methodology, and Sections 8.8 through 8.11 document the derivation of the eligible population denominators and the cost-per-incident-case figures applied throughout the cost-savings model. Readers seeking the primary evidence base and methodological detail underpinning the Section 7 model outputs are directed to these appendix sections.

3 TARGET POPULATION

The cost-savings model is applied to a precisely defined eligible population derived from two primary criteria: an age boundary restricting analysis to adults aged 55 and above, and an intervention-specific risk factor criterion, elevated fasting triglycerides for Omega-3 EPA+DHA, and elevated total cholesterol including familial hypercholesterolaemia for Phytosterols and Beta-Glucan. The rationale for both criteria, including the methodological justification for the 55-plus age boundary over the broader 40–79 trial population range, is documented in full in Section 8.10.

3.1 Age boundaries

The 55-plus restriction is applied for three reinforcing reasons: consistency between the MACE incidence denominator and the eligible population denominator, concentration of IHD and stroke incidence in this age cohort, and closer demographic alignment with the mean participant age of approximately 60–65 in the source RCTs. Restricting to 55-plus is a conservative choice, absolute risk reduction per person is larger in older populations with higher baseline event rates, meaning the applied RRR parameters if anything understate supplementation efficiency in this group.

3.2 Population size and eligible denominators

Across the EU27+UK in 2025, the eligible population is approximately 34.6 million adults for Omega-3, representing 20% of the 173 million adults aged 55 and above, and approximately 83.7 million adults for Phytosterols and Beta-Glucan, representing 49% of the 55-plus population. The Phytosterols and Beta-Glucan denominator is constructed as the sum of adults aged 55 and above with elevated total cholesterol and adults aged 55 and above with familial hypercholesterolaemia, with the derivation methodology for each component documented in Sections 8.8 and 8.9 respectively. The lower share for Omega-3 reflects the specificity of the elevated triglycerides criterion relative to the broader elevated total cholesterol denominator, not a smaller underlying prevention opportunity.[10]

3.3 Adoption scenarios

The model applies three coverage assumptions to distinguish between theoretical maximum value, sensitivity testing, and realistic near-term uptake. The 100% eligible population coverage scenario is used as the primary ceiling case. It represents the maximum addressable economic value if all eligible adults adopted the relevant intervention at the modelled dose. This should not be interpreted as a forecast of real-world uptake. A 30% coverage scenario is presented as a near-term adoption case, reflecting a more realistic population penetration assumption for public health and market planning purposes. A 50%

[10] The eligible population denominator applies the WHO/ESC borderline-high threshold of ≥1.7 mmol/L (≥150 mg/dL), which is marginally more conservative than the ≥1.5 mmol/L (≥135 mg/dL) REDUCE-IT trial enrolment threshold. See Section 7.1.3 for full methodological rationale.

coverage scenario is retained as an intermediate sensitivity test to demonstrate the linear relationship between coverage, avoided events, gross healthcare cost savings, and net benefit. Because supplementation costs and healthcare cost savings scale proportionally with the number of users reached, readers can derive additional uptake scenarios by applying alternative coverage assumptions to the 100% coverage outputs presented in Section 7.

3.4 Forecast to 2035

The eligible population grows only modestly over the projection window, from 34.60 million in 2025 to 34.60 million in 2035 for Omega-3, and from 83.75 million to 83.97 million for Phytosterols and Beta-Glucan, as demographic ageing in Western Europe is largely offset by population contraction in 15 Eastern and Southern European countries, including Latvia (−10.9%), Lithuania (−8.3%), Bulgaria (−7.7%), and Romania (−6.1%). The near-stability of the eligible population denominators means that the growth in gross HCCS and net benefit across the projection window is driven primarily by rising healthcare unit costs rather than by population expansion, as documented in Section 7.2.4. Full country-level eligible population projections from 2025 to 2035 are set out in Section 8.10.

4 OMEGA-3 (EPA + DHA) SUPPLEMENTS CVD RISK REDUCTION PATHWAY

The following table summarises the key clinical trials underpinning the omega-3 EPA+DHA efficacy analysis in this report. Full methodology and evidence synthesis are presented in Sections 4.1 through 4.5.

Study	Population	Intervention and dose	Follow-up	Primary outcome	Key result
REDUCE-IT (Bhatt et al., 2019)	8,179 statin-treated patients with hypertriglyceridaemia, established CVD or diabetes	Icosapent ethyl 4 g/day vs mineral oil placebo	Median 4.9 years	5-point MACE	25% RRR (HR 0.75; 95% CI 0.68–0.83)
STRENGTH (Nicholls et al., 2020)	13,078 statin-treated patients with mixed dyslipidaemia	Omega-3 carboxylic acids 4 g/day vs corn oil placebo	Terminated early (median 3.5 years)	5-point MACE	No significant MACE reduction (HR 0.99; 95% CI 0.90–1.09)
JELIS (Yokoyama et al., 2007)	18,645 Japanese hypercholesterolaemic patients on statins	Purified EPA 1.8 g/day vs control	Mean 4.6 years	Major coronary events	19% RRR (HR 0.81; 95% CI 0.69–0.95)
ASCEND (ASCEND Study Collaborative Group, 2018)	15,480 adults with diabetes, no prior CVD	Omega-3 1 g/day vs olive oil placebo	Mean 7.4 years	Serious vascular events	11% RRR (RR 0.89; 95% CI 0.80–1.00; p=0.055), borderline significance
VITAL (Manson et al., 2019)	25,871 adults without prior CVD	Omega-3 1 g/day vs placebo	Median 5.3 years	Major cardiovascular events	No significant reduction in primary endpoint; 28% RRR in MI (HR 0.72; 95% CI 0.59–0.90)
OMEMI (Kalstad et al., 2021)	1,027 elderly post-MI patients aged 70–82	Omega-3 1.8 g/day vs corn oil placebo	2 years	5-point MACE	No significant reduction in primary endpoint; elevated AF signal (HR 1.88; 95% CI 1.02–3.48)
Yan et al. 2024 meta-regression	Pooled 15 trials, 149,051 participants	Combined EPA+DHA 0.4–4 g/day	Various	MACE, MI, CVD death, AF, stroke, bleeding, cancer	5% MACE RRR per 1 g/day (RR 0.95; 95% CI 0.92–0.98); 9% AF increment per 1 g/day

4.1 Overview

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain n-3 polyunsaturated fatty acids derived primarily from marine sources. Its use as nutritional intervention is supported by direct randomised controlled trial evidence of cardiovascular event reduction.

The contemporary evidence base is anchored by Yan et al.[11], a systematic review and meta-analysis of 15 RCTs covering 141,164 participants across general, diabetic, high-risk CVD, established CVD, and post-MI

[11] Cardiovascular Drugs and Therapy (2024) 38:799–817

populations, with an average follow-up of 4.2 years and evidence quality assessed using the GRADE framework[12] (Grading of Recommendations Assessment, Development and Evaluation). This represents the most comprehensive and rigorously stratified analysis of omega-3 supplementation and cardiovascular outcomes currently available.

The CVD risk reduction pathway for omega-3 EPA+DHA is multifactorial. Two primary biomarker-mediated mechanisms have been extensively characterised in the clinical literature: triglyceride lowering, which addresses residual lipid risk not captured by LDL-C management, and blood pressure reduction, which operates through endothelial and vascular mechanisms. Both pathways are supported by meta-analytic evidence and operate independently of and additively to statin-mediated LDL-C reduction. Both pathways contribute to the composite MACE relative risk reduction applied in the cost-savings model. They are not modelled as separate parallel cost streams; rather, their combined clinical effect is captured implicitly in the composite MACE RRR parameter derived from the Yan et al. 2024 dose-response meta-regression, which reflects outcomes observed across RCT populations in which both mechanisms were operative. The mechanistic narrative in Sections 4.3 and 4.4 documents these pathways for scientific completeness and to establish the biological plausibility of the modelled RRR, not as independent inputs to the cost calculation. Beyond these two primary pathways, omega-3 EPA+DHA exerts a range of pleiotropic effects including atherosclerotic plaque stabilisation, anti-inflammatory activity through suppression of the NF-κB cascade, and antithrombotic effects through inhibition of thromboxane A2, mechanisms that collectively contribute to the cardiovascular event reduction observed in RCT evidence.

A critical methodological consideration for this report is the distinction between dietary supplement formulations and high-dose pharmaceutical omega-3 preparations. While omega-3 EPA+DHA is not classified as a prescription medicine in the EU, and all commercially available omega-3 products in the EU market are food supplements, certain cardiovascular outcome trials were conducted using pharmaceutical-grade icosapent ethyl at 4 g/day, which exceeds the EFSA-endorsed safe upper level of 3,000 mg/day for food supplements. For clarity, this report uses the term 'high-dose pharmaceutical preparation' rather than 'prescription dose' when referring to these trial formulations. As Yan et al. 2024 demonstrates, the magnitude of cardiovascular event reduction differs substantially by formulation type and dose, and this distinction has direct implications for how efficacy estimates are applied in the economic model. This issue is addressed in detail in the clinical evidence and modelling sections that follow.[13]

To ensure methodological consistency and transparency, the clinical evidence for omega-3 EPA+DHA supplementation is framed using the PICOS framework, defining the Population, Intervention, Comparator, Outcomes, and Study design parameters that govern the evidence reviewed and the assumptions applied in the economic model. This framework makes explicit the boundaries of the analysis, including the target population, the supplement dose and formulation type modelled, the primary and secondary outcomes assessed, and the adverse signals that are incorporated as offsets in the cost-savings calculation.

[12] Standardised framework used to assess the certainty of evidence in clinical research and systematic reviews.

[13] The REDUCE-IT trial enrolled patients with fasting triglycerides ≥1.5 mmol/L (≥135 mg/dL). The eligible population denominator applied in the cost-savings model uses the more conservative WHO/ESC threshold of ≥1.7 mmol/L; see Section 7.1.3 for rationale.

Despite the well-documented cardiovascular benefits of omega-3 EPA+DHA, most of the EU adult population has chronically suboptimal omega-3 status.[14] Population-level assessments using the Omega-3 Index, the percentage of EPA+DHA in red blood cell membranes, the most validated biomarker of long-term omega-3 tissue status, consistently show that most European adults fall in the range of 4–5%, well below the cardioprotective threshold of 8% established by Harris and Von Schacky (2004) and subsequently confirmed across prospective cohort analyses.[15] This low baseline status persists despite the availability of omega-3-rich dietary sources including oily fish, walnuts, flaxseed, and omega-3-enriched vegetable oils, reflecting the fact that habitual dietary intake across the EU27+UK remains insufficient to achieve and maintain cardioprotective tissue concentrations in most adults.

Crucially, because omega-3 EPA+DHA obtained from food contributes to the same tissue pool as omega-3 obtained from supplements, supplementation acts additively rather than substitutively relative to dietary intake: individuals with higher dietary omega-3 intake require smaller supplemental doses to reach a given Omega-3 Index target, while those with low dietary intake, the majority of the EU27+UK eligible population, derive greater marginal benefit from supplementation.

This additive relationship is directly relevant to the eligible population denominator applied in the cost-savings model: adults aged 55 and above with elevated fasting triglycerides are, by definition, a subgroup in which triglyceride-lowering omega-3 EPA+DHA activity is most clinically meaningful, and this group is also least likely to be achieving adequate omega-3 intake through diet alone given that elevated triglycerides are themselves a marker of suboptimal lipid metabolism that omega-3 EPA+DHA directly addresses.

4.2 Primary CVD event outcomes

The cardiovascular event reduction evidence supporting the interventions assessed in this report differs by ingredient. For Omega-3 EPA+DHA, the evidence base includes randomised controlled trials and meta-analyses directly evaluating cardiovascular outcomes, with dose-response analyses supporting the MACE relative risk reductions applied in the model. For Phytosterols and Beta-Glucan, direct cardiovascular outcomes trials are more limited; their estimated effects on MACE are therefore derived from their established LDL-C-lowering effects and translated into cardiovascular risk reduction using the Gould et al. (2007) and Ference et al. (2012, 2017) risk translation framework.

This report presents five modelling scenarios across the three interventions assessed. For Omega-3 EPA+DHA, the base-case scenario applies a 5.0% MACE relative risk reduction (RRR) at 1,000 mg/day and an enhanced scenario applies a 9.0% MACE RRR at 2,000 mg/day, derived from the dose-response meta-regression reported by Yan et al. (2024). For Phytosterols, the base-case scenario applies a 7.0% MACE RRR at 1.5 g/day and an enhanced scenario applies a 12.0% MACE RRR at 3.0 g/day, derived from LDL-C reductions reported by Demonty et al. (2009) and translated into cardiovascular event reduction using the Gould et al. (2007) and Ference et al. (2012, 2017) risk translation framework. For Beta-Glucan, a single

[14] Schuchardt et al. (2024), "Omega-3 world map: 2024 update," Progress in Lipid Research, 95:101286

[15] Harris WS, von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? Preventive Medicine. 2004;39(1):212–220.

scenario applies a 6.4% MACE RRR at 3.0 g/day, derived from LDL-C reductions reported by Llanaj et al. (2022) and translated using the same cardiovascular risk reduction framework.

The 1,000 mg/day Omega-3, 1.5 g/day Phytosterol, and 3.0 g/day Beta-Glucan scenarios are modelled as the primary base-case interventions. The higher-dose Omega-3 and Phytosterol scenarios are presented as enhanced efficacy cases to illustrate the potential economic impact associated with greater risk-factor reduction. All scenarios are modelled across the EU27+UK population from 2025 to 2035 under identical epidemiological, demographic, and economic assumptions.

This report presents five modelling scenarios reflecting the clinically relevant dose ranges and evidence base for the three interventions assessed. For Omega-3 EPA+DHA, the base-case scenario applies a 5.0% MACE relative risk reduction (RRR) at 1,000 mg/day and an enhanced scenario applies a 9.0% MACE RRR at 2,000 mg/day, derived from the dose-response meta-regression reported by Yan et al. (2024). For Phytosterols, the base-case scenario applies a 7.0% MACE RRR at 1.5 g/day and an enhanced scenario applies a 12.0% MACE RRR at 3.0 g/day, derived from LDL-cholesterol reductions reported by Demonty et al. (2009) and translated into cardiovascular event reduction using the Gould et al. (2007) and Ference et al. (2012, 2017) risk translation framework. For Beta-Glucan, a single scenario applies a 6.4% MACE RRR at 3.0 g/day, derived from LDL-cholesterol reductions reported by Llanaj et al. (2022) and translated using the same cardiovascular risk reduction framework.

The 1,000 mg/day Omega-3, 1.5 g/day Phytosterol, and 3.0 g/day Beta-Glucan scenarios are modelled as the primary base-case interventions, reflecting intake levels that are broadly aligned with current commercial availability, consumer use patterns, and the underlying evidence base. The higher-dose Omega-3 and Phytosterol scenarios are presented as enhanced efficacy cases to illustrate the potential economic impact associated with greater risk-factor reduction. All scenarios are modelled across the EU27+UK population from 2025 to 2035 under identical epidemiological, demographic, and economic assumptions.

A structural limitation of the evidence chain for Phytosterols and Beta-Glucan is that their modelled MACE risk reductions are not derived directly from cardiovascular outcomes trials. Instead, observed LDL-C reductions are translated into estimated cardiovascular event reductions using the Gould et al. (2007) and Ference et al. (2012, 2017) risk translation framework. The resulting MACE RRRs should therefore be interpreted as modelled estimates based on the established relationship between LDL-C reduction and cardiovascular risk, rather than as directly observed event reductions in primary prevention food supplement trials.

4.3 Dose-response relationship, Major Adverse Cardiovascular Events (MACE)

The clinical evidence reviewed in this section spans a range of omega-3 formulations, doses, and EPA:DHA ratios, and it is important to characterise these parameters explicitly before applying efficacy estimates to the economic model.

The studies informing the Yan et al. 2024 meta-regression cover combined EPA+DHA interventions at doses ranging from 0.4g to 3.84g/day, with EPA:DHA ratios varying across the included trials from approximately 1:1 in standard combined fish oil formulations to EPA-only preparations at the high-dose pharmaceutical

end of the range. The base-case and enhanced dose scenarios modelled in this report, 1,000 mg/day and 2,000 mg/day of combined EPA+DHA, fall within this studied range and are directly consistent with commercially available EU food supplement formulations, which typically provide EPA and DHA in ratios of approximately 3:2 to 2:1 (EPA:DHA) at doses of 500–2,000 mg/day per capsule or recommended daily intake. This contrasts with high-dose pharmaceutical preparations such as icosapent ethyl (Vascepa), which delivers 4g/day of EPA as an ethyl ester, an EPA-only formulation at a dose exceeding the EFSA-endorsed safe upper level of 3,000 mg/day for food supplements, and which is not available as a food supplement in the EU.

Where this report references REDUCE-IT trial results (Bhatt et al. 2019, 25% MACE RRR), these are presented solely to illustrate the upper bound of the EPA dose-response continuum and to contextualise the food supplement model estimates; they are not used as inputs to the base-case or enhanced scenario RRR parameters, which are derived exclusively from the Yan et al. 2024 dose-response meta-regression applied to combined EPA+DHA at food supplement doses.

The Yan et al. meta-regression is the most important quantitative update for the economic model. Across the dose range of 0.4g to 3.84g/day, each additional 1g of n-3 fatty acids was associated with a 5% reduction in MACE RR (RR 0.95; 95% CI 0.92–0.98; p=0.006), and this dose-response relationship explained 77.8% of the heterogeneity in MACE outcomes. This is a linear relationship confirmed using both stated dose and actual free fatty acid dose. The practical implication for the model is that a food supplement providing approximately 0.8–1.0g/day of actual free EPA+DHA would be expected to yield a MACE RR reduction of approximately 4–5% per the dose-response regression, consistent with the 2016 report's 4.9% RRR estimate derived from a different methodological route. This convergence across independent analytical approaches strengthens the credibility of the base case efficacy assumption.

For atrial fibrillation, the dose-response relationship runs in the opposite direction: each additional 1g of n-3 fatty acids increases AF risk by 9% (RR 1.09; 95% CI 1.01–1.18; p=0.006), with the relationship confirmed on actual free fatty acid dose (RR 1.09; 95% CI 1.00–1.19; p=0.048). This is linear across the 0.84–3.84g/day range. No dose-response relationship was detected for cardiovascular death (R^2=0%), meaning the mortality benefit does not scale with dose in the same way and is less predictable at food supplement doses.

4.4 Mechanistic pathways

The cardiovascular risk reduction associated with omega-3 EPA+DHA supplementation operates through two primary biomarker-mediated pathways, triglyceride lowering and blood pressure reduction, and a set of secondary mechanisms that contribute to the overall event reduction observed in RCT evidence.

All pathways operate independently of and additively to statin-mediated LDL-C reduction, positioning EPA+DHA as a complementary rather than redundant intervention in statin-treated populations, and as a standalone risk reduction tool in individuals who are statin-naïve (individuals who have never taken statin medication to lower cholesterol) or statin-intolerant.

4.4.1 Triglyceride-lowering pathway

EPA reduces plasma triglycerides through a hepatic mechanism: activation of peroxisome proliferator-activated receptor alpha (PPAR-α) and inhibition of sterol regulatory element binding protein-1 (SREBP-1), which together suppress the expression of proteins involved in very low-density lipoprotein (VLDL) synthesis and promote mitochondrial and peroxisomal beta-oxidation of fatty acids. The net effect is a reduction in the hepatic assembly and secretion of triglyceride-rich VLDL particles into the circulation.

The quantified magnitude of this effect at food supplement doses is established by Wang et al.., a continuous dose-response meta-analysis of 90 RCTs, which confirms an approximately linear relationship between combined EPA+DHA intake and triglyceride reduction across the dose range relevant to this report. At approximately 1,000 mg/day of actual free EPA+DHA, the base case food supplement dose modelled in this report, triglyceride reduction from baseline is approximately −0.25 to −0.30 mmol/L, rising to −20–30% from baseline at 2,000 mg/day, the EU-authorised health claim threshold for triglyceride maintenance under EU Regulation (EC) No 1924/2006, and up to −45% in hypertriglyceridaemic populations at high pharmaceutical doses above 3,000 mg/day. . Calder et al., in an updated systematic review of nine RCTs comparing near-pure EPA and DHA at doses of ≥2 g/day, confirms that both fatty acids lower triglyceride levels, with DHA most likely having a marginally greater effect, while EPA demonstrates superior plaque-stabilising and anti-inflammatory properties.

This effect is clinically effective in the EU27+UK target population. As documented in Section 2, mean baseline fasting triglyceride levels across the study geography sit at or above 1.7 mmol/L, the WHO borderline-high threshold, across the majority of Member States, and the proportion of adults aged 40–79 with fasting triglycerides ≥2.0 mmol/L is substantial, particularly in Central and Eastern European countries that record the highest composite cardiovascular risk scores in the Frost & Sullivan index. A reduction of 0.25–0.30 mmol/L at the 1g/day base case dose constitutes a meaningful reduction in residual cardiovascular risk through the VLDL-mediated atherogenic pathway, independent of any LDL-C effect.

4.4.2 Blood pressure reduction pathway

EPA and DHA reduce blood pressure through several converging vascular mechanisms: promotion of endothelial nitric oxide bioavailability, which mediates vasodilation; modulation of calcium signalling in vascular smooth muscle cells; regulation of the epithelial sodium channel in the kidney, enhancing sodium excretion; and inhibition of thromboxane A2-mediated vasoconstriction. The combined effect is a reduction in peripheral vascular resistance that translates into measurable reductions in both systolic and diastolic blood pressure.

The quantified dose-response for this pathway is established by Zhang et al.[16], a meta-analysis of 71 RCTs covering 4,973 participants across a dose range of 0.2 to 15g/day. At the 1,000 mg/day food supplement base case dose, the modelled systolic blood pressure reduction is approximately −1.5 to −2.0 mmHg, consistent with the lower bound of the Zhang et al. dose-response curve. At 2,000 mg/day, the enhanced scenario modelled in this report and the EU-authorised health claim threshold for triglyceride maintenance,

[16] Zhang X et al., Journal of the American Heart Association. 2022;11(11):e025071.

systolic blood pressure reduction reaches approximately −2.0 to −2.6 mmHg and diastolic blood pressure reduction reaches −1.8 mmHg. At 3,000 mg/day, the EU-authorised health claim threshold for blood pressure maintenance under EU Regulation (EC) No 1924/2006, the effect is greatest in hypertensive patients, with systolic blood pressure reductions approaching −4 mmHg.

Critically for the geographic stratification of the FSE cost model, Zhang et al. demonstrates that the blood pressure-lowering effect is significantly amplified in higher-risk subgroups: adults with baseline systolic blood pressure ≥130 mmHg, adults aged ≥45, and adults with concurrent hyperlipidaemia all show greater responses than the overall trial population mean. These characteristics describe the majority of the target population across the EU27+UK as documented in Section 2, where mean systolic blood pressure sits above 130 mmHg in most of the Member States and hypertension diagnosis prevalence reaches 44.1% in Eastern Europe. Countries including Bulgaria, Romania, Latvia, Lithuania, Poland, and Slovakia, which record both the highest systolic blood pressure burdens and the highest composite CVD risk scores in the Section 2 analysis, therefore represent the geographies where the blood pressure pathway generates the greatest modelled cost savings per supplementation user.

At population scale, a 2 mmHg reduction in mean systolic blood pressure across the eligible EU27+UK hypertensive population is associated with a clinically meaningful reduction in stroke and coronary event incidence, providing the quantitative basis for the blood pressure component of the cost model developed in Section 5.

4.4.3 Additional cardiovascular protective effects

Beyond the two primary modelled pathways, EPA and DHA have several additional protective effects on the cardiovascular system that contribute to the overall event reduction observed in RCT evidence:

- EPA stabilises atherosclerotic plaque by increasing fibrous cap thickness and reducing plaque vulnerability, as demonstrated in coronary imaging studies.[17,18]
- EPA delays disease progression by suppressing the NF-κB inflammatory cascade[19], reducing the expression of pro-inflammatory cytokines and adhesion molecules that drive atherosclerotic plaque formation and rupture[20].
- EPA and DHA have antithrombotic effects[21] through competitive inhibition of arachidonic acid metabolism and reduction in thromboxane A2 production, reducing platelet aggregation and thrombotic risk.

[17] Nelson JR et Al., Vascular Pharmacology. 2017;91:1–9.

[18] Cawood AL et Al., Atherosclerosis. 2010;212(1):252–9.

[19] Welty FK et Al., Translational Research. 2016;167(1):257–80.

[20] Yan J et Al., Cardiovascular Drugs and Therapy. 2024;38:799–817.

[21] Sheikh O et al., Cardiovascular Diabetology. 2019;18(1):84.

- EPA also promotes the release of specialised pro-resolving mediators[22] including resolvins and protectins, which actively resolve inflammatory states rather than merely suppressing them.[23]

These distinct biological mechanisms reinforce the benefits delivered through triglyceride lowering and blood pressure reduction, though they are not independently modelled in the cost-savings framework given the absence of sufficiently granular dose-response data to isolate their individual contributions.

These mechanisms are consistent with the cardiovascular event reductions observed in JELIS and REDUCE-IT, and provide biological plausibility for the overall RRR parameter applied in the cost model, even where individual pathway contributions cannot be precisely isolated at food supplement doses.

4.5 Safety profile and updated risk quantification

Yan et al. 2024 confirms that omega-3 n-3 fatty acids are broadly safe across the three primary safety endpoints examined in the meta-analysis. At food supplement doses up to 3,000 mg/day, the EFSA-endorsed upper level for combined EPA+DHA in adults, no elevated cancer risk, no elevated bleeding risk, and no clinically significant gastrointestinal adverse effects were identified. High-dose pharmaceutical O3AEE demonstrated a particularly clean gastrointestinal profile (RR 1.01; 95% CI 0.97–1.05), indistinguishable from placebo, and no formulation was associated with an elevated cancer risk across the 141,164 participants included in the analysis (RR 1.03; 95% CI 0.98–1.09; p=0.204). Dietary supplement formulations were not associated with elevated bleeding risk. The one dose-dependent safety signal at food supplement doses is atrial fibrillation, for which the meta-regression identifies a 9% incremental increase in risk per additional 1 g/day of n-3 fatty acids across the 0.84–3.84 g/day range; this signal is quantified and incorporated as a cost offset in the economic model as described below. These findings support the general tolerability of omega-3 EPA+DHA supplementation at food supplement doses and are consistent with the safety profile observed across decades of clinical trial evidence.

Alongside its cardiovascular benefits, Yan et al. 2024 identifies two specific health risks associated with omega-3 supplementation that generate their own healthcare costs, Atrial fibrillation and Stroke risk in post-MI patients. These costs must be subtracted from the gross cardiovascular savings projected in the economic model as if ignored, the model would overstate the true financial benefit of supplementation. Both risks are strongly dependent on dose and formulation type, and as shown below, their financial impact at the food supplement doses modelled in this report is substantially smaller than the headline risk figures suggest. A third signal, elevated bleeding risk with prescription EPA ethyl ester, does not affect the food supplement model directly but carries implications for the policy framing of the report's conclusions.

[22] Mason RP et Al., Biomedicine and Pharmacotherapy. 2018;103:1231–7.

[23] Sherratt SCR, et al., Prostaglandins, Leukotrienes and Essential Fatty Acids, Volume 173, October 2021, 102337

4.5.1 Atrial fibrillation

Atrial fibrillation is an irregular heart rhythm in which the upper chambers of the heart lose their normal coordinated beat and quiver rather than pump efficiently. Blood can pool in the heart and form clots that, if dislodged, travel to the brain causing stroke or to the heart causing myocardial infarction. AF events generate direct healthcare costs through acute hospitalisation, cardioversion procedures, and initiation of long-term anticoagulant therapy, and they reduce quality of life through persistent symptoms including palpitations, breathlessness, and fatigue.

The pooled AF risk across all formulations and doses in the Yan et al. 2024 analysis is RR 1.25 (95% CI 1.10–1.41; p<0.001), with moderate heterogeneity (I^2=57.4%). This signal persists after excluding STRENGTH, the trial identified as the primary source of heterogeneity: RR 1.17 (95% CI 1.07–1.29; p=0.001). The AF risk applies in patients both with and without established CVD.

The dose-response meta-regression in Yan et al. 2024 establishes that AF risk increases by 9% for each additional 1 g/day of n-3 fatty acids (RR 1.09; 95% CI 1.01–1.18; p=0.006), a linear relationship confirmed using actual free fatty acid dose across the 0.77–3.5 g/day range. The pooled RR of 1.25 therefore reflects a weighted average across trials conducted at doses substantially higher than the food supplement base case, including REDUCE-IT at 4 g/day and STRENGTH at 4 g/day O3CA. At the base case food supplement dose of approximately 1,000 mg/day of actual free EPA+DHA, the dose-response regression implies an incremental AF risk of approximately RR 1.09 relative to placebo, meaning that for every 100 cardiovascular events avoided through MACE reduction, approximately 9 additional AF hospitalisations are generated, a ratio that is explicitly offset in the net benefit calculation. No threshold dose below which AF risk is entirely absent has been identified; the signal is present from the lowest dose in the meta-regression range (0.84 g/day) and increases linearly thereafter. At the enhanced scenario dose of 2,000 mg/day, the implied AF RR rises to approximately 1.18, requiring a proportionally larger offset. The model therefore presents the AF cost offset as an explicit line item in the net benefit calculation at both dose scenarios, ensuring the offset is transparent and auditable rather than absorbed silently into a net figure.

The mechanism underlying the AF signal is not fully resolved. Yan et al. 2024 notes that n-3 fatty acids inhibit fast sodium channel current and slow L-type calcium channel current in cardiomyocytes in a concentration-dependent manner, leading to shortening of action potential duration and slowing of action potential conduction, effects that may be both antiarrhythmic and proarrhythmic depending on the electrophysiological context. Whether long-term supplementation leads to myocardial fibrosis and structural atrial changes remains an open research question.

4.5.2 Stroke risk in post-MI patients

A stroke occurs when blood supply to part of the brain is cut off, causing brain cells to begin dying within minutes. Consequences range from temporary weakness or confusion through to permanent disability, paralysis, loss of speech, cognitive impairment, and death. Stroke events are among the most costly cardiovascular outcomes in the direct cost dataset, generating acute hospitalisation costs, long-term rehabilitation costs, and substantial productivity losses from permanent disability.

Yan et al. 2024 identified for the first time in a pooled meta-analytic dataset that supplementation with n-3 fatty acids is associated with an increased stroke risk specifically in patients with previous myocardial infarction (RR 1.32; 95% CI 1.04–1.68). This finding was not statistically significant in the overall stroke analysis across all population subgroups (RR 1.05; 95% CI 0.96–1.16; p=0.265), confirming that the elevated stroke risk is specific to the post-MI subpopulation rather than a class-wide effect applicable to the broader supplementing population.

The proposed mechanism is AF-mediated thromboembolism: the elevated AF risk in the post-MI subgroup, which records the highest AF signal of any population subgroup in the Yan et al. analysis (RR 1.88; 95% CI 1.02–3.48 in OMEMI, the dedicated post-MI trial), generates cardioembolic stroke events through ineffective atrial contraction and intra-atrial thrombus formation. This mechanistic link between the AF signal and the stroke signal in the post-MI population is biologically plausible and clinically important.

The direct implication for the economic model is that post-MI patients must be treated as a distinct subgroup with a separate net benefit calculation that explicitly offsets the stroke risk increment against the MACE and MI reduction benefits, rather than being pooled with the broader CVD risk factor population. In practice the eligible population is therefore segmented into two groups: a primary and mixed-risk prevention group, constituting the base case population for which gross healthcare cost savings are largest and the net benefit deficit is smallest at current supplement prices, and a post-MI subgroup for which the benefit-risk balance requires separate, more conservative modelling. Pooling post-MI patients with the broader population without this adjustment would overstate the net benefit of omega-3 supplementation for that subgroup and undermine the credibility of the overall model. The geographic dimension of this adjustment should also be noted: Western European countries with higher rates of surviving post-MI patients, reflecting better acute cardiac care and higher post-event survival, will be proportionally more affected by this population segmentation than Eastern European countries where the post-MI survivor pool is smaller relative to the primary prevention population. It should be noted that post-MI patients do not constitute a target group for food supplement intervention in the context of this report. The eligible population modelled throughout is defined as adults aged 55 and above with elevated triglycerides for Omega-3, who are not under active pharmaceutical cardiovascular management. Post-MI patients are typically under secondary prevention pharmacotherapy and fall outside this definition. The stroke risk signal identified by Yan et al. 2024 in the post-MI subpopulation is therefore noted for completeness and regulatory transparency but does not affect the primary cost-savings model.

4.5.3 Bleeding risk

At high pharmaceutical doses above 3,000 mg/day, EPA's antithrombotic inhibition of thromboxane A2, the compound that normally helps platelets clump together to seal wounds, becomes strong enough to meaningfully impair the body's normal clotting response. The practical consequences range from minor bleeds such as nosebleeds and bruising through to serious gastrointestinal bleeding and, in the most severe cases, haemorrhagic stroke. The risk is compounded in patients concurrently taking anticoagulant medications such as warfarin or novel oral anticoagulants.

High-dose pharmaceutical EPA ethyl ester carries a significantly elevated bleeding risk relative to other formulations (RR 1.50; 95% CI 1.13–1.99). This signal is specific to pharmaceutical-grade EPA ethyl ester formulations used at high doses in cardiovascular outcome trials, principally Vascepa at 4 g/day as used in REDUCE-IT and Epadel at 1.8 g/day as used in JELIS, and does not apply to food supplement O3AEE or to the food supplement doses modelled in the base case (1,000 mg/day) or enhanced scenario (2,000 mg/day) of this report. Yan et al. 2024 does not identify a dose threshold below which the bleeding signal definitively disappears, but the absence of a significant bleeding signal in food supplement O3AEE trials is consistent with the lower EPA concentrations and different excipient profiles of supplement-grade preparations. The bleeding signal therefore requires no direct cost offset in the economic model.

Two practical points follow from this.

1. Even the higher dose modelled in this report (2,000 mg/day) remains well below the pharmaceutical threshold at which the bleeding risk signal appears, so no bleeding cost needs to be deducted from the model at any dose scenario examined.

2. If the report's conclusions are used to advocate for higher-dose supplementation, any such recommendation should clearly state that bleeding risk increases at pharmaceutical-level doses above 3,000 mg/day, particularly for individuals already taking blood-thinning medications.

5 PHYTOSTEROLS SUPPLEMENTS CVD RISK REDUCTION PATHWAY

5.1 Overview

Plant sterols and stanols, collectively referred to as phytosterols, are naturally occurring compounds found in vegetable oils, nuts, seeds, and cereals, structurally analogous to cholesterol.[24]

Commercial phytosterol blends are dominated by beta-sitosterol (60–70%), campesterol (16–30%), and stigmasterol (3–10%), alongside stanol variants sitostanol and campestanol. At supplementation doses of 1.5 to 3.0 grams per day, phytosterols reduce LDL-cholesterol, the primary causal driver of atherosclerotic cardiovascular disease, by between 7% and 12.5%, an effect confirmed across more than 140 randomised controlled trials and formally recognised by the European Food Safety Authority under Regulation EU 432/2012.

Among the three nutritional interventions examined in this report, phytosterols, beta-glucans, and omega-3 EPA+DHA, phytosterols have the most precisely characterised dose-response relationship: a log-linear curve established across 124 RCTs with an R^2 exceeding 0.99,[25] independently validated by EFSA at specific quantitative thresholds,[26] and consistent across food-format and supplement delivery vehicles.[27]

The dose of 1.5–3.0 grams per day is at the upper range of what is practically achievable through conventional food supplement capsule formats, and the primary commercial delivery vehicles for phytosterols in the EU market are accordingly fortified functional foods rather than capsule supplements, notably fortified spreads, yoghurt drinks, and cereal bars, which allow the required daily dose to be incorporated naturally into habitual dietary patterns.

The dose-response evidence base and the EU-authorised health claim apply equally to phytosterol-enriched functional foods and to capsule supplement formats, as the LDL-C lowering effect is driven by the phytosterol molecule irrespective of the food matrix in which it is delivered.

The supplement cost methodology applied in this report uses a per-gram ingredient cost of €0.31, which is consistent across both delivery formats and is validated by industry assessment[28] suggesting a typical market average of approximately €0.26/g, confirming the base-case cost assumption is conservative for phytosterols. For the purposes of the cost-savings model, the term "supplementation" encompasses both encapsulated supplement products and fortified functional food formats delivering the modelled phytosterol dose.

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[24] Stellaard & Lütjohann, (2025), Phytosterol-Enriched Dietary Supplements for Lowering Plasma LDL-Cholesterol: Yes or No?, Nutrients 2025, 17, 654

[25] Demonty I, Ras RT, van der Knaap HC, Duchateau GS, Meijer L, Zock PL, Plat J, Mensink RP. Continuous dose-response relationship of the LDL-cholesterol-lowering effect of phytosterol intake. Journal of Nutrition. 2009;139(2):271–284.

[26] 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. EFSA Journal. 2012;10(5):2693. The disease risk reduction claim for plant stanol esters is authorised under Commission Regulation (EU) No 432/2012.

[27] Ras RT et al., LDL-cholesterol-lowering effect of plant sterols and stanols across different dose ranges: a meta-analysis of randomised controlled studies. British Journal of Nutrition. 2014;112(2):214–219

[28] FSE member company assessment (2026)

Among the three interventions, both phytosterols and beta-glucan hold EU-authorised claims linking their consumption to a reduction in the risk of coronary heart disease under Commission Regulation (EU) No 432/2012. The authorised claim for plant stanol esters explicitly states a reduction in the risk of coronary heart disease. Oat and barley beta-glucan carry authorised claims stating that their consumption contributes to the maintenance of normal blood cholesterol levels, with the EU regulatory framework explicitly recognising that maintaining normal cholesterol levels reduces the risk of coronary heart disease. Omega-3 EPA+DHA holds an authorised cardiac function claim at 250 mg/day but does not carry a disease risk reduction claim under the same regulation.

Beyond LDL-C lowering, emerging meta-analytic evidence suggests that phytosterol supplementation may exert a secondary cardioprotective effect through modest blood pressure reduction. A systematic review and meta-analysis of 19 RCTs by Ghaedi et al. (2020)[29] demonstrated statistically significant reductions in both systolic BP (WMD: −1.55 mmHg, 95% CI: −2.67 to −0.42, p = 0.007) and diastolic BP (WMD: −0.84 mmHg, 95% CI: −1.60 to −0.08, p = 0.03). While modest in absolute terms, this finding is clinically relevant in the context of population-level modelling: the Prospective Studies Collaboration has established that each 1 mmHg reduction in systolic BP corresponds to approximately a 2.5% age- and sex-specific reduction in vascular mortality. The BP effect is therefore treated in this report as a secondary supportive pathway, noted but not double-counted in the primary cost-savings projection. At the same time, phytosterols are the subject of an unresolved scientific debate about whether supplementation-induced elevation of plasma phytosterol concentrations may independently contribute to atherosclerosis risk, a question this section addresses directly and transparently.

Unlike omega-3 EPA+DHA, for which direct RCT evidence of cardiovascular event reduction is available at high-dose pharmaceutical preparation levels (see Section 4), phytosterols have no long-term cardiovascular outcome trial. The cost-savings model for phytosterols therefore relies on a two-step inference: from LDL-C reduction to cardiovascular event risk reduction, using the Mendelian randomisation-calibrated risk translation model of Ference et al.(2012, 2017)[30,31] as the validated bridge between surrogate endpoint and projected clinical outcome.[32] This is the same modelling framework applied to beta-glucans in the following section, and its assumptions, limitations, and sensitivity analyses are described in the modelling methodology section.

[29] Ghaedi E. et al., Effects of phytosterols supplementation on blood pressure: A systematic review and meta-analysis, Clinical Nutrition 39 (2020) 2702e2710

[30] Ference BA et al., Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *Journal of the American College of Cardiology*. 2012;60(25):2631–2639.

[31] Ference BA et al., Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. European Heart Journal. 2017;38(32):2459–2472.

[32] A surrogate-to-outcome inference framework is an analytical process of estimating a clinical outcome, in this report, a reduction in heart attacks, strokes, or cardiovascular death, from a measured change in a biological marker rather than from directly observed event data.

5.2 Primary CVD event outcomes

No dedicated long-term randomised cardiovascular outcome trial exists for phytosterols, a gap explicitly acknowledged by major European cardiology societies, including the German Cardiac Society, which has formally called for such trials to be conducted (Makhmudova et al.,[33] 2021; Athyros et al., 2023[34]).

This is the central evidentiary limitation of this intervention and distinguishes it from omega-3 EPA+DHA, for which the REDUCE-IT trial (Bhatt et al., 2019)[35] and subsequent meta-analyses provide direct MACE evidence at high-dose pharmaceutical preparation levels.

Phytosterols are classified exclusively as food ingredients and novel foods in the EU and are not available as prescription medicines; there is therefore no pharmaceutical-grade phytosterol preparation against which a cardiovascular outcome trial has been or could readily be conducted within the EU regulatory framework. The absence of an outcome trial for phytosterols reflects a structural feature of the nutritional supplementation regulatory environment rather than a specific evidentiary failure: because phytosterols are classified as food ingredients rather than medicinal products, the regulatory pathway that would require or incentivise a multi-year cardiovascular outcome trial has never applied. The same limitation affects beta-glucans. The evidence chain linking phytosterol supplementation to cardiovascular event risk reduction is instead constructed from two well-established and independently validated components.

The first is the quantified reduction in circulating LDL-cholesterol produced by phytosterol supplementation at recommended doses, established across more than 140 randomised controlled trials.[36] LDL-C is the primary causal driver of atherosclerotic plaque formation: elevated concentrations accelerate the deposition of cholesterol in arterial walls, the inflammatory response that destabilises plaques, and the thrombotic events, myocardial infarction and ischaemic stroke, that constitute the clinical endpoints this model projects. Reducing LDL-C therefore directly attenuates the biological process generating those events, not merely a statistical correlate of it.

The second is the causal relationship between LDL-C reduction and cardiovascular event risk, established through Mendelian randomisation studies, which exploit naturally occurring genetic variation in LDL-C levels as a natural experiment free of confounding, and through the Cholesterol Treatment Trialists (CTT) meta-analyses, which demonstrate a consistent 22% relative reduction in major vascular events per 1.0 mmol/L reduction in LDL-C, independent of the mechanism by which LDL-C is reduced.[27,28] Ference et al. (2012) + Ference et al. (2017) Critically, Ference et al. (2012) demonstrated using Mendelian randomisation that genetic variants producing lifelong modest reductions in LDL-C via NPC1L1 inhibition, the same absorption pathway targeted by phytosterols, are associated with proportionate reductions in coronary

[33] Makhmudova U et al. Phytosterols and cardiovascular disease. Current Atherosclerosis Reports. 2021;23(10):59

[34] Athyros VG et al. Plant sterols and stanols in cholesterol management and cardiovascular prevention. Nutrients. 2023;15(7):1809.

[35] Bhatt et al., Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia, N Engl J Med 2019;380:11-22

[36] Fontané L. et al., Use of phytosterol-fortified foods to improve LDL cholesterol levels: A systematic review and meta-analysis, Nutr Metab Cardiovasc Dis, 2023 Aug;33(8):1472-1480.

heart disease risk, providing the closest available mechanistic analogue to phytosterol supplementation in human genetics. This finding directly supports the validity of applying the CTT risk translation coefficient to phytosterol-mediated LDL-C reductions.

The projected cardiovascular event reduction underpinning the cost-savings model in this report is therefore not a direct observation but a model-derived estimate: the observed LDL-C reduction at the recommended supplementation dose, translated through the Gould et al. (2007) / Ference et al. (2012, 2017) risk bridge, applied to the EU27+UK eligible population with appropriate discounting for real-world adherence and population heterogeneity. The transparency of this inference chain is a deliberate feature of the report's analytical approach.

NICE has consistently maintained this position across successive guideline iterations, from CG181 (2014) through to NG238 (2023),[37,38] recommending that individuals at increased risk of CVD not be advised to take plant stanols or sterols as part of their cholesterol-lowering strategy, precisely because the population-level event reduction evidence that our model is designed to quantify has not previously been available.

5.3 Dose-response relationship, Major Adverse Cardiovascular Events (MACE)

The Yan et al. meta-regression is the most important quantitative update for the economic model. Across the dose range of 0.4g to 3.84g/day, each additional 1g of n-3 fatty acids was associated with a 5% reduction in MACE RR (RR 0.95; 95% CI 0.92–0.98; p=0.006), and this dose-response relationship explained 77.8% of the heterogeneity in MACE outcomes. This is a linear relationship confirmed using both stated dose and actual free fatty acid dose. The practical implication for the model is that a food supplement providing approximately 0.8–1.0g/day of actual free EPA+DHA would be expected to yield a MACE RR reduction of approximately 4–5% per the dose-response regression, consistent with the 2016 report's 4.9% RRR estimate derived from a different methodological route. This convergence across independent analytical approaches strengthens the credibility of the base case efficacy assumption.

For atrial fibrillation, the dose-response relationship runs in the opposite direction: each additional 1g of n-3 fatty acids increases AF risk by 9% (RR 1.09; 95% CI 1.01–1.18; p=0.006), with the relationship confirmed on actual free fatty acid dose (RR 1.09; 95% CI 1.00–1.19; p=0.048). This is linear across the 0.84–3.84g/day range. No dose-response relationship was detected for cardiovascular death (R^2=0%), meaning the mortality benefit does not scale with dose in the same way and is less predictable at food supplement doses.

5.4 Mechanistic pathways

Phytosterols reduce circulating LDL-C through competitive inhibition of intestinal cholesterol absorption. Structurally analogous to cholesterol, phytosterols are incorporated into intestinal micelles with high

[37] Cardiovascular disease: risk assessment and reduction, including lipid modification - Clinical guideline, Reference number: CG181, Published: 18 July 2014

[38] Cardiovascular disease: risk assessment and reduction, including lipid modification - NICE guideline Reference number:NG238, Published: 14 December 2023

efficiency, competing with cholesterol for incorporation and thereby reducing the fraction of both dietary and biliary cholesterol available for absorption into the enterohepatic circulation. Within the enterocyte, phytosterols interact poorly with the NPC1L1 cholesterol uptake transporter and are actively re-secreted into the intestinal lumen by ABCG5/G8 transport proteins, a mechanism that simultaneously limits their own systemic absorption to less than 5% while reducing cholesterol uptake. The consequent fall in hepatic cholesterol delivery triggers compensatory upregulation of LDL receptor expression on hepatocyte membranes, accelerating the clearance of circulating LDL particles. The net effect is a reduction in LDL-C with no meaningful effect on HDL-C or triglycerides (Stellaard and Lütjohann, 2025).

Because phytosterols act at the absorption stage rather than the synthesis stage, their LDL-C lowering effect is additive to that of statins, a property confirmed across multiple combination studies and referenced in current ESC/EAS dyslipidaemia guidelines as a rationale for combination use in statin-intolerant patients or those not reaching LDL-C targets on statin therapy alone.

The proposed mechanism for the blood pressure effect operates through a separate pathway. Ghaedi et al. (2020) suggest that phytosterols may stimulate prostacyclin release from vascular smooth muscle cells, a potent vasodilator that reduces peripheral vascular resistance and arterial stiffness. An indirect contribution through LDL-C lowering itself is also plausible, given that cholesterol reduction is associated with improved endothelial function and reduced large artery stiffness. These mechanistic pathways are consistent with the observed BP reductions but remain incompletely characterised, and the authors note that the exact mechanism has not yet been established through dedicated mechanistic study.

This mechanistic complementarity to statins is directly relevant to the population defined in this report's cost-savings model. The target population, adults with mild-to-moderately elevated LDL-C who are not currently receiving pharmacotherapy, represents the pre-statin intervention space. In this population, phytosterol supplementation operates as a standalone LDL-C lowering intervention through the absorption pathway.

The mechanistic pathway for beta-glucans, described in the next section, overlaps partially with phytosterols at the intestinal level but operates through viscosity-mediated bile acid sequestration rather than direct micellar competition. The two mechanisms are partially complementary. The modelling framework treats them as operating in separate, non-overlapping subpopulations to avoid double-counting.

5.5 Safety profile and updated risk quantification

The tolerability profile of phytosterol supplementation at recommended doses of 1.5–3.0 g/day is well-established and materially favourable, and is formally underpinned by the EU novel food authorisation of phytosterol and stanol esters. Plant sterol and stanol esters were originally authorised as novel foods under Regulation (EC) No 258/97 following a dedicated EFSA safety evaluation, and this authorisation has been maintained under the current novel foods framework, Regulation (EU) 2015/2283, confirming that the safety profile at authorised doses has been reviewed and accepted by EU regulators. Across more than 140 clinical trials, no significant adverse effects on liver enzymes, renal function, hormonal parameters, or fat-soluble vitamin absorption have been consistently identified at doses within the EU-authorised range. Gastrointestinal effects, nausea, constipation, mild diarrhoea, are reported infrequently and are typically

mild and self-limiting. This tolerability profile is substantially better than that of prescription statins, which carry myopathy and hepatotoxicity signals. Extensive safety evaluation studies have found no evidence of mutagenic activity or toxicity at supplementation doses (Ghaedi et al., 2020).

One nutritional consideration is the potential for phytosterols to modestly reduce serum concentrations of fat-soluble vitamins and carotenoids. Under Regulation (EU) No 1169/2011 on the provision of food information to consumers, products containing added phytosterols are subject to mandatory labelling requirements advising consumers to maintain adequate fruit and vegetable intake as part of a varied diet, in order to help maintain carotenoid levels. This regulatory safeguard means that the carotenoid reduction effect is flagged to consumers at the point of purchase and does not represent an unmanaged safety signal at population-level supplementation doses.

The unresolved safety question for phytosterols concerns plasma phytosterol concentrations rather than gastrointestinal tolerability. Supplementation raises plasma concentrations of beta-sitosterol and campesterol, and observational and Mendelian randomisation data have generated conflicting signals about whether elevated plasma phytosterols are independently associated with cardiovascular risk.

The most recent and most rigorous assessment of this question, Stellaard and Lütjohann (2025), concludes that the available evidence does not support a causal atherogenic role for phytosterols at concentrations achievable through food supplement doses of 1.5–3.0 g/day, and that the dominant effect of phytosterol supplementation at these doses remains LDL-C reduction with a net cardioprotective direction of effect. The authors note that earlier observational associations between plasma phytosterol concentrations and cardiovascular events may reflect confounding by dietary patterns rather than a causal atherogenic signal from phytosterols themselves.

The cost-savings model in this report does not apply an adverse event offset for the plasma phytosterol signal, consistent with the Stellaard and Lütjohann (2025) conclusion that net cardiovascular effect remains beneficial at supplement doses. This assumption is tested in sensitivity analysis: the conservative scenario applies a 15% discount to the projected net benefit to reflect residual uncertainty around the plasma phytosterol question, and this discount is explicitly reported alongside the base case projection. This approach mirrors the methodology applied for the atrial fibrillation offset in the omega-3 model, ensuring analytical consistency across all three interventions.

For context on the relative magnitude of the safety signals across the three interventions: omega-3 EPA+DHA at high pharmaceutical doses carries a quantified AF risk signal (RR 1.25 pooled, rising with dose per Yan et al. 2024) that is explicitly modelled as a cost offset in the economic model, noting that at the food supplement doses modelled in this report (1,000 mg/day base case, 2,000 mg/day enhanced scenario) the AF signal is present but proportionally smaller, as described in Section 4.5; phytosterols carry an unresolved and likely non-causal plasma concentration signal that is handled through a conservative sensitivity discount; beta-glucans carry no identified safety signal beyond mild transient gastrointestinal effects at the 3 g/day EFSA dose.

5.6 Section 5 Summary: Phytosterols evidence base and economic implications

The clinical and economic case for phytosterol supplementation rests on a well-characterised LDL-C reduction pathway, a robust regulatory foundation, and a transparent handling of the one unresolved safety question. Four key findings underpin the model. First, the Demonty et al. (2009) meta-analysis of 84 trials establishes a precise, nonlinear dose-response relationship with a pooled LDL-C reduction of 8.8% at the mean trial dose of 2.15 g/day, the strongest and most precisely characterised efficacy parameter of the three interventions in this report. Second, the Gould et al. (2007) / Ference et al. (2012, 2017) risk translation bridge converts this LDL-C reduction to a projected 7% MACE RRR at the 1,500 mg/day base-case dose, a conservative estimate that is robust across sensitivity analyses. Third, the absence of a long-term cardiovascular outcome trial for phytosterols is a structural feature of the EU food ingredient regulatory environment rather than a scientific gap unique to this intervention, and is addressed transparently through surrogate-to-outcome inference with explicit sensitivity analysis. Fourth, the plasma phytosterol elevation signal does not support causality at supplement doses per the most recent evidence, but is nonetheless handled through a conservative 15% sensitivity discount. Phytosterols generate the largest absolute net benefit of the three interventions, driven by the combination of a large eligible population and a very low SC/HCCS ratio of 0.052.

6 BETA-GLUCAN SUPPLEMENTS CVD RISK REDUCTION PATHWAY

6.1 Overview

Beta-glucans are soluble polysaccharides composed of glucose units linked by β-1,3 and β-1,4 glycosidic bonds, occurring naturally in the cell walls of oats and barley. At a supplementation dose of 3 grams per day, the threshold formally reviewed and authorised by the European Food Safety Authority under Commission Regulation EU 432/2012, oat and barley beta-glucan reduces LDL-cholesterol by approximately 0.29 mmol/L in populations with mildly-to-moderately elevated cholesterol, an effect confirmed across more than 70 randomised controlled trials and consistent across European and non-European study populations (Llanaj et al., 2022).[39]

Among the three nutritional interventions examined in this report, phytosterols, beta-glucans, and omega-3 EPA+DHA, beta-glucans occupy a clearly defined and stable regulatory position, but a more modest evidence base than phytosterols in terms of dose-response precision and a narrower mechanistic evidence chain than omega-3 in terms of direct cardiovascular event data.

Oat and barley beta-glucan carry EU-authorised health claims under Commission Regulation (EU) No 432/2012, supported by EFSA scientific opinions issued in 2009 and 2011 (EFSA NDA Panel, EFSA Journal 2009;7(9):1254 and EFSA Journal 2011;9(6):2207). These claims state that beta-glucan contributes to the maintenance of normal blood cholesterol levels, with the EU regulatory framework explicitly recognising that maintaining normal cholesterol levels reduces the risk of coronary heart disease, a disease risk reduction pathway analogous to that underpinning the phytosterol claim. No long-term cardiovascular outcome trial exists for beta-glucan. The cost-savings model for beta-glucans therefore applies the same surrogate-to-outcome inference framework used for phytosterols: LDL-C reduction translated to projected MACE reduction using the Ference et al. / Cholesterol Treatment Trialists risk bridge, with conservative effect size assumptions and explicit sensitivity analysis.

Beta-glucans are mechanistically complementary to but distinct from phytosterols. Both interventions operate in the intestinal lumen, but through different pathways. Phytosterols reduce cholesterol absorption through direct micellar competition at the NPC1L1 transporter; Beta-glucans act through viscosity-mediated disruption of bile acid reabsorption, forcing increased hepatic bile acid synthesis from endogenous cholesterol and thereby upregulating LDL receptor activity. Because the mechanisms are partially additive rather than identical, the cost-savings model treats the two interventions as operating in distinct, non-overlapping subpopulations to avoid double-counting.

[39] Llanaj E. et al., Effect of oat supplementation interventions on cardiovascular disease risk markers: a systematic review and meta-analysis of randomized controlled trials, European Journal of Nutrition (2022) 61:1749–1778

6.2 Primary CVD event outcomes

As with phytosterols, no dedicated long-term cardiovascular outcome trial exists for beta-glucan supplementation. This is the central evidentiary limitation of this intervention. The absence of an outcome trial reflects the same structural feature of the nutritional regulatory environment noted for phytosterols: food ingredient classification does not create the regulatory incentive structure that drives pharmaceutical companies to conduct multi-year event trials. This limitation is shared with phytosterols and is handled through the same modelling approach.

The evidence chain connecting beta-glucan supplementation to cardiovascular event risk reduction is constructed from two components. The first is the quantified reduction in circulating LDL-cholesterol produced by beta-glucan supplementation at recommended doses, established across more than 70 randomised controlled trials and detailed in the phytosterols section. LDL-C is the primary causal driver of atherosclerotic plaque formation: elevated concentrations accelerate the deposition of cholesterol in arterial walls, the inflammatory response that destabilises plaques, and the thrombotic events, myocardial infarction and ischaemic stroke, that constitute the clinical endpoints this model projects. Reducing LDL-C therefore directly attenuates the biological process generating those events, not merely a statistical correlate of it. The second component is the established causal relationship between LDL-C reduction and cardiovascular event risk, documented through the Cholesterol Treatment Trialists meta-analyses and the Mendelian randomisation work of Ference et al. (2012, 2017). As described in Section 5.2, the CTT evidence demonstrates a consistent 22% relative reduction in major vascular events per 1.0 mmol/L reduction in LDL-C, independent of the mechanism by which that reduction is achieved.

One distinction from phytosterols is worth noting here. For phytosterols, Ference et al. (2012) identified a specific genetic analogue, NPC1L1 variants mimicking ezetimibe-type absorption inhibition, that closely parallels the phytosterol mechanism. For beta-glucans, the mechanistic parallel is less direct: beta-glucan's LDL-C lowering operates primarily through bile acid sequestration and secondary upregulation of LDL receptor activity rather than direct NPC1L1 competition. The CTT risk translation coefficient is nonetheless applicable, as it captures the relationship between LDL-C reduction and cardiovascular event risk regardless of the upstream mechanism.

NICE (2014) concluded that there is evidence that foods containing plant sterols and stanols reduce cholesterol, but insufficient long-term evidence that these reduce cardiovascular events at a population level, a conclusion that extends analogously to beta-glucans. Our cost-saving model is designed explicitly to quantify the projected population-level event reduction that this evidence gap has left uncharacterised.

6.3 Dose-response relationship, Major Adverse Cardiovascular Events (MACE)

The dose-response relationship for beta-glucan-mediated LDL-C reduction is well-established but less precisely characterised than that of phytosterols. Where phytosterols have a log-linear dose-response curve with an R^2 exceeding 0.99 across 124 RCT arms, the beta-glucan evidence base yields a more variable picture, with efficacy moderated by molecular weight, viscosity, food matrix, and processing conditions in ways that prevent a single, clean dose-response curve of equivalent statistical precision.

The most comprehensive meta-analytic evidence is provided by Llanaj et al. (2022, European Journal of Nutrition),[40] a systematic review and meta-analysis of 74 RCTs including 4,937 participants. Across the 12 trials in the primary comparison, beta-glucan supplementation versus oat-free control, the pooled LDL-C reduction was −0.29 mmol/L (95% CI: −0.37 to −0.20) and total cholesterol reduction was −0.42 mmol/L (95% CI: −0.61 to −0.22), both statistically significant and stable on leave-one-out sensitivity analysis.[41] These effect sizes are consistent regardless of dietary background, including Mediterranean-diet-adherent populations, a finding of direct relevance to the EU27+UK modelling context, where background dietary fibre intake varies substantially across countries.

The BELT Study (Cicero et al., 2020, Nutrients)[42] provides the most rigorous single-trial evidence at precisely the EU-authorised dose of 3g/day in a European population. In 83 Italian adults with mild hypercholesterolaemia adherent to a Mediterranean diet, a high-molecular-weight oat beta-glucan formulation (>2,000 kDa) reduced LDL-C from baseline by 12.2% at 4 weeks and 15.1% at 8 weeks ($p<0.01$ versus placebo), corresponding to an absolute reduction of 0.59 mmol/L. Total cholesterol fell 8.9% and non-HDL-C 12.1% at 8 weeks. These effect sizes exceed the EFSA minimum reference estimate of approximately 7–10% LDL-C reduction, a discrepancy attributable to the very high molecular weight of the tested preparation. High-molecular-weight beta-glucan generates greater luminal viscosity, more effectively impairs bile acid reabsorption, and consistently achieves larger LDL-C reductions than medium or low molecular weight preparations, a finding with direct implications for product quality assessment in any population-level supplementation programme.

A critical practical observation from the BELT study is that the LDL-C effect reversed to baseline within two weeks of stopping supplementation. This reversibility distinguishes beta-glucan from the longer-lasting effects of statins and has a direct bearing on the cost-savings model's adherence assumptions: sustained long-term supplementation is required for projected savings to be realised, and the model's adherence trajectories are calibrated accordingly.

For the cost-savings model, the base case LDL-C reduction is set at −0.29 mmol/L, drawn from the Llanaj et al. 2022 pooled estimate across 74 RCTs. This is the more conservative of the two available anchors and is preferred for the base case because it reflects a broad and heterogeneous evidence base spanning multiple beta-glucan sources, molecular weights, food matrices, and study durations, making it more representative of real-world supplement use at population level than the BELT study estimate. The Llanaj et al. meta-analysis includes trials conducted at 3 g/day and above; the average study duration across included trials was approximately 6–8 weeks, consistent with the timeframe over which the LDL-C effect is established. The higher BELT study figure of −0.59 mmol/L reflects a specifically high-molecular-weight oat formulation

[40] Llanaj E. et al., Effect of oat supplementation interventions on cardiovascular disease risk markers: a systematic review and meta-analysis of randomized controlled trials, European Journal of Nutrition (2022) 61:1749–1778

[41] Statistical method used in meta-analyses to test whether the pooled result is being disproportionately driven by any single study in the dataset.

[42] Cicero A. et al., A Randomized Placebo-Controlled Clinical Trial to Evaluate the Medium-Term Effects of Oat Fibers on Human Health: The Beta-Glucan Effects on Lipid Profile, Glycemia and inTestinal Health (BELT) Study, Nutrients. 2020 Mar 3;12(3):686

(>2,000 kDa) under controlled Mediterranean-diet conditions and is applied in the enhanced scenario as the upper-bound estimate, not discarded. The difference between the two anchors is therefore not a contradiction but a reflection of the well-documented molecular-weight dependency of beta-glucan efficacy. Applying the Gould et al. (2007) / Ference et al. (2012, 2017) risk translation coefficient of 22% relative MACE reduction per 1.0 mmol/L LDL-C reduction yields a model-derived MACE relative risk reduction of approximately 6.4% at the base case. The enhanced scenario uses the BELT study estimate of −0.59 mmol/L, yielding a projected MACE RRR of approximately 13%. Both scenarios assume the EU-authorised dose of 3 g/day. As with phytosterols, every point on the beta-glucan MACE dose-response curve is model-derived rather than directly observed, and this is addressed through sensitivity analysis.

6.4 Mechanistic pathways

The cardiovascular risk reduction associated with omega-3 EPA+DHA supplementation operates through two primary biomarker-mediated pathways, triglyceride lowering and blood pressure reduction, and a set of secondary mechanisms that contribute to the overall event reduction observed in RCT evidence.

All pathways operate independently of and additively to statin-mediated LDL-C reduction, positioning EPA+DHA as a complementary rather than redundant intervention in statin-treated populations, and as a standalone risk reduction tool in individuals who are statin-naïve (individuals who have never taken statin medication to lower cholesterol) or statin-intolerant.

6.4.1 Mechanistic complementarity with phytosterols and clinical evidence for additivity

The mechanistic relationship between beta-glucans and phytosterols is central to understanding both their individual and combined effects. Both interventions operate intestinally but through entirely distinct primary steps:

- **Phytosterols act at the micellar incorporation stage**, competing with cholesterol for inclusion into bile acid micelles and limiting the fraction of dietary and biliary cholesterol available for uptake at the NPC1L1 transporter, with ABCG5/G8 actively re-secreting absorbed phytosterols back into the intestinal lumen.

- **Beta-glucan acts upstream, at bile acid reabsorption and CYP7A1 upregulation**, without directly competing at NPC1L1. The downstream consequence, LDL receptor upregulation and accelerated LDL-C clearance, is shared, but the rate-limiting steps are distinct and non-competing.

Because the mechanisms are distinct, they are additive rather than redundant when combined. This theoretical additivity is confirmed by the most rigorous available clinical evidence. Ferguson et al. (2020, Clinical Nutrition),[43] in a double-blinded, placebo-controlled 2×2 factorial RCT in 72 hypercholesterolaemic adults, tested 3g/day high-MW oat beta-glucan (2,000–2,500 kDa) and 2g/day phytosterols individually and in combination against placebo over 6 weeks. LDL-C was reduced by 8.6% in the beta-glucan arm, 7.6% in

[43] Ferguson et al. High molecular weight oat β-glucan enhances lipid-lowering effects of phytosterols. A randomised controlled trial, Clin Nutr. 2020 Jan;39(1):80-89

the phytosterol arm, and 13.9% in the combination arm, with two-way ANOVA confirming an additive rather than synergistic interaction, precisely as the distinct mechanistic pathways predict. The combined reduction in total cholesterol (−11.5%) was significantly greater than either intervention alone and significantly greater than placebo ($p<0.001$). These findings validate both the mechanistic framework and the cost-savings model's treatment of the two interventions as operating through distinct, non-interfering pathways that can each be independently projected without risk of double-counting.

The Ferguson et al. findings also have a practical implication beyond the modelling framework. In populations where both phytosterol and beta-glucan supplementation is accessible, which applies across the EU27+UK given both are available as food supplements and authorised under Regulation EU 432/2012, sequential or concurrent use could realistically achieve combined LDL-C reductions in the 12–14% range from nutritional supplementation alone, approaching the lower end of statin-equivalent effects without the hepatic and myopathic adverse event profile. This positions the combination as a particularly relevant adjunct or alternative therapy for the statin-intolerant population, a segment explicitly noted by Ferguson et al. as a clinical application warranting further investigation.

6.4.2 Secondary mechanistic pathway: gut microbiome modulation

Beta-glucan that escapes small intestinal digestion reaches the colon intact, where it functions as a selective fermentable substrate for commensal bacteria. Ayivi-Tosuh et al. (2026)[44] characterise the gut microbiome as a complex, dynamic ecosystem whose health depends on the balance between SCFA-producing commensals and pro-inflammatory LPS-producing species, with microbial-associated molecular patterns (MAMPs), including lipopolysaccharides, peptidoglycans, and flagellins, signalling through pattern recognition receptors to modulate both local intestinal immunity and systemic inflammatory tone.

Beta-glucan's prebiotic activity selectively promotes the growth of SCFA-producing commensals, while reducing the relative abundance of LPS-producing pro-inflammatory species, generating two cardiovascular consequences that operate independently of and additively to the primary LDL-C lowering pathway.

The first consequence is metabolic.

The dominant SCFA products of beta-glucan fermentation, propionate and butyrate, exert direct effects on cholesterol metabolism. Propionate mildly inhibits hepatic HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis targeted by statins. Butyrate inhibits histone deacetylase (HDAC) activity in intestinal epithelial cells, modulating expression of cholesterol transport proteins including NPC1L1 and further reducing absorptive capacity for dietary cholesterol (Qu et al., 2024).[45] These effects reinforce the primary bile acid sequestration mechanism through a complementary and parallel pathway. Ferguson et al. (2020)

[44] "Ayivi-Tosuh SM et al., Gut-Microbiome Interactions: Characterization, Therapeutic Implications and Machine Learning, Sage Open Pathol. 2026 Feb 5;19:30502098251415109"

[45] Qu J et al., Unlocking Cardioprotective Potential of Gut Microbiome: Exploring Therapeutic Strategies, J. Microbiol. Biotechnol. 2024. 34(12): 2413–2424

note explicitly that beta-glucan's promotion of colonic SCFA production is one of the additional health benefits that makes beta-glucan an attractive complement to phytosterol therapy beyond the direct cholesterol-lowering effects.

The second consequence is anti-inflammatory.

Ayivi-Tosuh et al. (2026) document that dysbiosis drives chronic low-grade systemic inflammation through MAMP-mediated immune activation, elevated circulating endotoxin, and compromised gut barrier integrity, a pathway that accelerates atherosclerotic plaque formation and destabilisation independently of LDL-C levels. Beta-glucan supplementation attenuates this pathway by shifting microbiome composition toward SCFA-producing commensals that strengthen gut barrier function and suppress the inflammatory signalling associated with atherosclerosis progression. The magnitude of this anti-inflammatory benefit is subject to substantial interindividual variability and is conservatively omitted from the primary cost-savings projection.

6.5 Safety profile and updated risk quantification

The safety and tolerability profile of oat beta-glucan supplementation at and above the EU-authorised dose of 3g/day is well-established and consistently favourable across multiple trial designs, populations, and durations.

Across the 74 trials reviewed in Llanaj et al. (2022), no significant adverse effects on liver enzymes, renal function, blood pressure, or glycaemic markers were consistently identified at any dose. The BELT study (Cicero et al., 2020) assessed safety prospectively in 83 subjects over 8 weeks with laboratory monitoring at each visit and found no adverse laboratory changes at any timepoint. Mild gastrointestinal effects were reported in four subjects, three with transient abdominal cramps or diarrhoea and one with transient dysphagia, none of which led to trial discontinuation. Treatment compliance was 89%.

Iman et al. (2025)[46] adds confirmatory safety and tolerability evidence from a separate 12-week randomised crossover trial in 21 mildly hypertensive middle-aged and older adults consuming 4g/day of high-molecular-weight oat beta-glucan. No harms or unintended effects were reported in any study group across the full 12-week duration. Minor gastrointestinal effects, increased flatulence in three participants, bloating in four, and accelerated digestion in two, were mild, non-serious, and caused no withdrawals. Compliance was 93%, the highest reported across comparable beta-glucan trials. Participants rated the oat treatment as relatively enjoyable and indicated willingness to consume a similar product commercially, a real-world acceptability signal directly relevant to the population-level uptake assumptions in the cost-savings model.

Ferguson et al. (2020) provides a further independent safety reference point, reporting excellent overall compliance of 98.24% across all four trial arms in 72 participants over 6 weeks, with the study biscuits well tolerated and no adverse events reported. Compliance in the beta-glucan-alone arm was 98.15%, consistent across the 6-week duration and with no significant gastrointestinal burden identified. Taken together, the three independent trials, BELT, Iman et al., and Ferguson et al., cover complementary

[46] Iman Y et al., Effect of oat β-glucan in managing blood pressure: a randomized cross-over pilot trial. Applied Physiology, Nutrition, and Metabolism. 2025;50:1–9. doi:10.1139/apnm-2024-0317.

populations and durations and collectively confirm a clean, consistent safety profile at 3–4g/day across 6–12 weeks in adults with hypercholesterolaemia, mild hypertension, and mixed cardiovascular risk profiles.

Comparative safety positioning across the three interventions

Beta-glucan carries none of the regulatory or mechanistic safety concerns that require explicit modelling treatment in the other two interventions. Unlike omega-3 EPA+DHA at high pharmaceutical doses, for which a quantified atrial fibrillation signal (RR 1.25, rising with dose per Yan et al., 2024) and a post-MI stroke signal (RR 1.32) are explicitly modelled as cost offsets, noting that at the food supplement doses modelled in this report these signals are proportionally smaller as described in Section 4.5, beta-glucan has no identified cardiovascular adverse signal at 3–4 g/day. Unlike phytosterols which carry an unresolved but likely non-causal concern about supplementation-induced plasma phytosterol elevation requiring a conservative 15% sensitivity discount in the cost-savings model, beta-glucan supplementation does not meaningfully raise plasma beta-glucan concentrations and generates no analogous structural concern.

Importantly, the Ferguson et al. (2020) combination trial confirms that co-administration of beta-glucan with phytosterols does not introduce any new safety signal. There is therefore no identified safety reason to avoid concurrent phytosterol and beta-glucan supplementation in populations where both are used, a consideration relevant to the model's non-overlapping population assumption: that assumption is a conservative analytical choice to avoid double-counting projected savings, not a reflection of any pharmacological incompatibility.

The only identified population-level safety consideration is the exclusion of individuals with inflammatory bowel disease, irritable bowel syndrome, or clinically significant dysphagia from the eligible population definition, given the potential for beta-glucan's viscosity-forming properties to exacerbate gastrointestinal symptoms in these conditions. This exclusion reduces the eligible population denominator by an estimated 3–5% relative to the total mild-to-moderate hypercholesterolaemia population, based on EU prevalence data for these conditions.

In terms of relative safety positioning across the three interventions: beta-glucan has the most straightforwardly favourable safety profile of the three, requiring no adverse event cost offset in the cost-savings model, no sensitivity discount for an unresolved mechanistic safety question, and no regulatory complexity of the kind that accompanies omega-3 at prescription doses.

This positions beta-glucan as the most analytically conservative of the three interventions from a net-benefit modelling perspective, its projected savings are not reduced by adverse event offsets, but its effect size is also the most modest and its MACE evidence chain is entirely model-derived rather than trial-observed.

6.6 Section 6 Summary: Beta-Glucan Evidence Base and Economic Implications

The clinical and economic case for beta-glucan supplementation is built on a well-validated LDL-C reduction mechanism, the most favourable safety profile of the three interventions, and a conservative modelling approach that explicitly acknowledges the molecular-weight dependency of the efficacy evidence. Four key

findings underpin the model. First, the Llanaj et al. (2022) meta-analysis of 74 RCTs establishes a pooled LDL-C reduction of 0.29 mmol/L at the EU-authorised dose of 3 g/day, which translates to a 6.4% MACE RRR via the Gould et al. (2007) / Ference et al. (2012, 2017) risk bridge. Second, the higher BELT study estimate of 0.59 mmol/L reflects a specifically high-molecular-weight formulation and is applied as the upper-bound enhanced scenario, confirming that product quality has a direct bearing on clinical efficacy. Third, beta-glucan carries no adverse event cost offset, no AF signal, no post-MI stroke signal, no plasma accumulation concern, making it the cleanest benefit-risk profile of the three interventions. Fourth, the combination trial evidence confirms that co-administration of beta-glucan with phytosterols introduces no new safety signal, supporting the modelling of all three interventions as independent and additive. Beta-glucan's higher per-user dose cost relative to phytosterols produces the highest SC/HCCS ratio of the three interventions at 0.206, but net benefit remains strongly positive in all 28 EU27+UK geographies.

7 COST-SAVINGS MODELLING

7.1 Research Methods

7.1.1 Model design and analytical approach

The model adopts a population-level prospective cost-benefit design, consistent with the methodological tradition established by the European Health Network-commissioned previous study (Shanahan et al. 2016/2017) and aligned with the health economic conventions set out in the European Commission's Better Regulation Guidelines. Rather than modelling individual patient-level outcomes, the analysis operates at the level of national eligible populations, translating published clinical efficacy estimates into projected changes in cardiovascular event incidence and the associated direct and indirect healthcare costs.

The core analytical structure follows a four-step sequence applied to each intervention independently:

1 - The eligible population is defined as the number of adults in each country meeting the eligibility criteria for each intervention across the projection window 2025 to 2035, drawn from Eurostat demographic projections and country-level cardiovascular risk factor prevalence data sourced from the IHME GBD 2023 dataset projected to the 2025 base year.

2 - A single-scenario population coverage assumption is applied: the entire eligible population is modelled as supplementing at the specified dose, compared against a counterfactual baseline of zero supplementation. No adoption rate or compliance discount is applied, the model is explicitly designed as a ceiling estimate of the maximum potential societal cost savings, quantifying the full economic opportunity if the eligible population were reached.

3 - The efficacy parameter for each intervention is applied to the supplemented eligible population to produce estimates of avoided incident MACE events by country and year, using the absolute risk reduction derived from the source epidemiological model and expressed as avoidable events equal to ARR multiplied by the eligible population denominator.

4 - Avoided events are monetised using country-level unit costs derived from the total CVD cost per incident case, encompassing healthcare and social care, informal care, and productivity losses, and net economic benefit is calculated as gross societal cost savings minus total supplementation costs, expressed as $B = S - C$.

The model produces results at two levels: country-level annual outputs for all 28 geographies across the projection window 2025 to 2035 and EU27+UK aggregate annual totals for each intervention. All monetary values are expressed in 2025 Euros, PPP-adjusted for cross-country comparisons, and a discount rate of 3.0% per annum is applied to future cost savings, consistent with EU health economic convention. A healthcare cost inflation rate of 2.8% per annum, derived from the Eurostat EU27 health expenditure compound annual growth rate over the 2015–2023 period, is applied to projected future event unit costs.

7.1.2 Efficacy parameters

Efficacy parameters are derived from the highest-quality available clinical evidence for each intervention, prioritising Cochrane-standard systematic reviews and meta-analyses of randomised controlled trials, supplemented by the EFSA scientific opinions that underpin authorised health claims in the European Union.

For Omega-3 EPA+DHA, the primary efficacy parameter is the relative risk reduction for major adverse cardiovascular events applied directly from RCT meta-analyses, as Omega-3 does not lower LDL-C and therefore does not operate through the LDL-C-to-event risk translation framework used for the other two interventions. The composite MACE RRR implicitly incorporates the cardiovascular benefits of both the triglyceride-lowering and blood pressure-reduction pathways, as these mechanisms were operative in the RCT populations from which the Yan et al. 2024 dose-response estimate is derived. TG and BP effects are therefore not modelled as separate cost streams; their combined clinical effect is captured implicitly in the composite MACE RRR parameter. For Phytosterols and Beta-Glucan, both of which exert their cardiovascular benefit primarily through LDL-C lowering, efficacy is parameterised as a percentage reduction in LDL-C, which is subsequently translated into a projected cardiovascular event risk reduction using the Mendelian randomisation-calibrated model of Ference et al. (2012). This framework estimates that a 1 mmol/L lifetime reduction in LDL-C corresponds to approximately a 22% relative risk reduction for major coronary events. For shorter-duration supplementation, the Gould et al. (2007) / Ference et al. (2012, 2017) coefficient provides a more conservative primary risk translation estimate, and this is applied as the base-case assumption with the Ference et al. figure used as the upper sensitivity bound.

The ARR, NNT, and avoidable event figures presented in this analysis correspond to the base-case dose for each intervention, 1,000 mg/day for Omega-3 EPA+DHA and 1,500 mg/day for Phytosterols, as embedded in the source epidemiological model. The 1,000 mg/day base-case dose for Omega-3 is consistent with the dose applied in the original 2016 Frost & Sullivan report (Shanahan, 2016), ensuring methodological continuity with the prior analysis. The enhanced scenario for Omega-3 applies 2,000 mg/day, corresponding to the EU-authorised health claim threshold for triglyceride maintenance under EU Regulation (EC) No 1924/2006. The EU-authorised health claim threshold for blood pressure maintenance is 3,000 mg/day; as the Yan et al. 2024 dose-response relationship is linear, the projected MACE RRR at 3,000 mg/day can be derived proportionally from the enhanced scenario outputs and approximates 15% under the base-case regression coefficient. This upper-bound estimate is not modelled separately as it falls at the EFSA safe upper level for combined EPA+DHA in food supplements and would require a proportionally larger AF cost offset. High-dose scenario results for Phytosterols (3,000 mg/day) are presented as sensitivity bounds in Section 7.2.3 and do not alter the primary model outputs. Beta-Glucan is modelled at a single fixed dose of 3,000 mg/day, consistent with the EU-authorised health claim threshold, and no high-dose sensitivity scenario is applied.

Country-level NNT values vary substantially across EU27+UK, ranging from approximately 44 in France to 69 in Malta for Omega-3 at the 2025 baseline, from 31 in France to 49 in Malta for Phytosterols, and from 34 in France to 54 in Malta for Beta-Glucan, reflecting differences in underlying baseline MACE incident rates rather than differences in intervention efficacy. Because ARR is defined as the product of the baseline event rate and the RRR, countries with higher CVD burden naturally produce lower NNT values, meaning fewer supplement users are required per avoided MACE eventa resource allocation advantage, not a difference in

the biological effect of the supplement, which is fixed by the RRR regardless of geography. This variation is methodologically expected and is consistent with how population-level cost-benefit models operate across heterogeneous health systems.

The full efficacy parameter specification is set out in the table below.

Parameter	Omega-3 EPA+DHA	Phytosterols	Beta-Glucan
Primary efficacy metric	MACE RRR (%)	LDL-C reduction (%)	LDL-C reduction (%)
Base-case dose	1,000 mg/day	1,500 mg/day	3,000 mg/day
High-dose / enhanced scenario	2,000 mg/day	3,000 mg/day	N/A, single dose
Base-case efficacy	5% MACE RRR	7% (~0.24 mmol/L)	~6.4% (~0.25 mmol/L)
High-dose efficacy	9% MACE RRR	12% (~0.44 mmol/L)	N/A
Risk translation method	Direct RRR from RCT meta-analyses	Gould et al. (2007) (base) / Ference et al. (2012, 2017) (upper)	Gould et al. (2007) (base) / Ference et al. (2012, 2017) (upper)
AF adverse event offset	RR 1.09 at 1g/day; RR 1.18 at 2g/day	None	None
Compliance discount	None, 100% coverage model	None	None
Primary evidence sources	Zhang et al. 2022; ASCEND 2018; STRENGTH 2020	EFSA 2012; Gylling et al. 2014; >140 RCTs	EFSA 2011; Ho et al. 2016 (14 RCTs, n=615); Whitehead et al. 2014

Table 7.1 Efficacy Parameters by Intervention

7.1.3 Population denominators

Eligible population denominators for each intervention are constructed from two primary data sources: Eurostat population projections by country, sex, and five-year age band covering the 2025 reference year and the 2035 projection endpoint; and country-level cardiovascular risk factor prevalence data from the European Society of Cardiology's SCORE2 dataset, the EAS Consensus Panel, and published European epidemiological surveys of lipid and triglyceride status. The eligible population for each intervention is defined as the subset of adults in each country who meet the relevant lipid or triglyceride eligibility criterion.

The eligible population for Omega-3 EPA+DHA is defined as adults aged 55 and above with elevated fasting triglycerides, the primary biological target of the triglyceride-lowering pathway that anchors the base-case RRR of 5%. This definition conservatively excludes adults with elevated systolic blood pressure but normal triglycerides, for whom the blood pressure reduction pathway of Omega-3 EPA+DHA supplementation,

documented by Zhang et al. 2022 to reduce SBP by 1.5 to 2.0 mmHg at 1g/day in populations with baseline SBP at or above 130 mmHg, is independently operative.[47]

For Phytosterols and Beta-Glucan, the denominator is the population with elevated total cholesterol, consistent with the LDL-C lowering mechanism of both interventions and the EU authorised health claim eligibility language. The two denominator populations are substantially distinct for Omega-3 versus the LDL-C interventions; however, the Phytosterol and Beta-Glucan eligible populations overlap considerably, as both draw from the same high total cholesterol risk stratum. The model treats these populations independently and does not assume additive event savings where the same individual may be counted in both denominators.

The use of elevated total cholesterol as the eligibility criterion for Phytosterols and Beta-Glucan, rather than elevated LDL-C directly, reflects four reinforcing considerations. First, harmonised country-level LDL-C prevalence data at the granularity required across all 28 EU27+UK geographies is not consistently available from a single authoritative source. The eligible PS/BG denominator is instead constructed as the sum of two components: adults aged 55 and above with elevated total cholesterol, and adults aged 55 and above with familial hypercholesterolaemia (FH), with the derivation methodology for each component documented in Sections 8.8 and 8.9 respectively. Second, elevated total cholesterol is a well-established proxy for elevated LDL-C in population-level epidemiological modelling; in the 55-plus population the proportion of individuals with elevated total cholesterol driven primarily by HDL-C rather than LDL-C is small, and the correlation between the two measures is sufficiently high to support total cholesterol as a valid screening threshold for LDL-C-lowering intervention. Third, the EU-authorised health claims underpinning both interventions reference reduction of blood cholesterol broadly rather than LDL-C specifically, making total cholesterol the more appropriate denominator criterion for claim-consistent population targeting. Fourth, this approach is if anything conservative: individuals whose elevated total cholesterol reflects predominantly HDL-C elevation are included in the denominator but are less likely to derive the full LDL-C-lowering benefit of supplementation, marginally diluting the modelled ARR relative to what would be observed in a denominator restricted to confirmed elevated LDL-C.

The denominator methodology is summarised in the Table 7.2 below.

[47] The elevated triglycerides threshold applied in this model is ≥1.7 mmol/L (≥150 mg/dL), consistent with the WHO and ESC/EAS borderline-high definition and the threshold used in population-level epidemiological datasets including the IHME GBD 2023 series. This is marginally more conservative than the ≥1.5 mmol/L (≥135 mg/dL) lower bound applied as an inclusion criterion in the REDUCE-IT trial (Bhatt et al., 2019), which enrolled patients with fasting triglycerides between 135 and 499 mg/dL. Applying the REDUCE-IT lower bound would modestly increase the eligible population denominator for Omega-3 and proportionally increase gross HCCS and net benefit estimates. The ≥1.7 mmol/L threshold is retained as the base-case criterion on the grounds that it reflects the standard clinical and epidemiological definition of borderline-high triglyceridaemia across the EU27+UK and is more appropriate for population-level modelling than a trial-specific enrolment threshold.

Parameter	Omega-3 EPA+DHA	Phytosterols	Beta-Glucan
Eligibility criterion	Elevated triglycerides	Elevated total cholesterol	Elevated total cholesterol
Risk factor data source	RISKS, High triglycerides	RISKS, High Total Cholesterol	RISKS, High Total Cholesterol
Population overlap with other interventions	Partially distinct	Substantially overlaps with Beta-Glucan	Substantially overlaps with Phytosterols
Treatment of overlap	Modelled independently	Modelled independently; no additive savings assumed	Modelled independently; no additive savings assumed
Geographic breakdown	28 countries; EU27+UK aggregate	28 countries; EU27+UK aggregate	28 countries; EU27+UK aggregate
Projection years	2025–2035	2025–2035	2025–2035

Table 7.2, Population Denominator Specification

7.1.4 Unit cost data

Unit cost data for cardiovascular events are drawn from the Luengo-Fernández et al. (2023) pan-European CVD economic burden dataset, supplemented by the European Heart Network economic burden report and WHO-CHOICE country-level healthcare unit cost estimates.

The cost per avoided event applied in the model is the total CVD cost per incident case, calculated as the total annual societal cost of CVD in each country divided by the annual number of incident MACE cases, encompassing healthcare and social care costs, informal care costs, and productivity losses.

This full societal perspective cost basis, rather than a narrower healthcare system perspective using H&SC costs alone, is used throughout as the primary metric, consistent with the analytical approach of Luengo-Fernández et al. and with the broader framing of the economic case for nutritional supplementation as a public health intervention. The choice of societal perspective produces a more comprehensive and defensible estimate of the economic opportunity; a sensitivity analysis using H&SC costs only is presented in Section 7.6. The cost per incident case is not a simple ratio of total CVD prevalence costs to new cases. The Luengo-Fernández et al. (2023) framework applies incidence-based episode costing, attributing costs to the acute event episode and the downstream treatment pathway initiated by that incident event. An avoided MACE event eliminates the acute hospitalisation cost, the cardiac rehabilitation pathway, the escalated pharmacotherapy cascade, the incremental informal care burden, and the associated productivity loss. It does not eliminate ongoing ambulatory management costs that would be incurred regardless of whether the event occurred, as these are captured in the prevalent-case cost pool rather than the incident-episode cost attribution. The cost per incident case therefore represents the economic footprint of the event episode, not the full lifetime cost of the resulting chronic CVD state. Reviewers applying an acute-hospitalisation-only cost definition should treat the H&SC-only sensitivity (Section 7.6) as the most conservative comparable benchmark.

7.1.5 Model scope and limitations

This model is designed to provide a transparent and policy-relevant estimate of the potential healthcare cost savings attributable to increased supplementation across the EU27+UK eligible population. It does not

constitute a full cost-effectiveness analysis or a Health Technology Assessment, and several important scope boundaries and analytical limitations are acknowledged below.

The most significant methodological limitation is the use of surrogate-to-event risk translation for the two LDL-C lowering interventions. The Mendelian randomisation framework calibrated by Ference et al. (2012) reflects the effect of lifetime LDL-C reduction, whereas supplementation in this context is taken for months to years rather than a lifetime. This distinction means the model's event reduction projections may overstate benefit relative to what would be observed in a shorter-duration real-world supplementation programme. The Gould et al. (2007) / Ference et al. (2012, 2017) coefficient is applied as the base case specifically to address this limitation, with the Ference et al. estimate used as the upper sensitivity bound. A second methodological consideration concerns cost attribution. The cost per avoided event applies the full incident-episode societal cost, encompassing acute hospitalisation, the downstream treatment pathway, informal care, and productivity loss, derived from the Luengo-Fernández et al. (2023) incidence-based framework. This is the appropriate perspective for a full societal cost-savings analysis. Reviewers applying a narrower acute-event-only cost definition should note that the H&SC-only sensitivity in Section 7.6 addresses this, reducing combined net benefit to €111.2 billion. The base-case figures represent the ceiling of the defensible range under the full societal perspective; the H&SC-only figures represent the floor under the healthcare payer perspective.

The second limitation is that the model is a ceiling estimate by design. The 0% versus 100% population coverage comparison quantifies the maximum achievable benefit under ideal conditions; it does not forecast expected real-world uptake. Policymakers and commercial readers should interpret results as the economic opportunity available, not as a projection of what will be realised under current market conditions. A 50% population coverage sensitivity scenario, which halves all avoidable event and cost savings outputs proportionally, is available as a reference point for more conservative planning assumptions.

The high-dose sensitivity scenarios for Omega-3 (2,000 mg/day, RRR 9%) and Phytosterols (3,000 mg/day, LDL-C reduction 12%) are presented as enhanced scenarios generating materially larger net benefit than the base case, as documented in Section 7.2.3. The Omega-3 high-dose estimate is anchored on the Yan et al. 2024 dose-response meta-regression coefficient applied to the incremental gram from 1g to 2g/day, yielding a 9% MACE RRR, rather than the REDUCE-IT trial result of approximately 25% MACE RRR at 4,000 mg/day prescription-grade icosapentaenoic acid ethyl ester, which is not applicable to dietary supplement formulations at 2,000 mg/day. This distinction should be borne in mind when interpreting the enhanced scenario outputs in Section 7.3.

For Omega-3 supplementation, an adverse event offset for atrial fibrillation is explicitly incorporated. Yan et al. (2024) identified an AF risk increment of RR 1.09 at 1,000 mg/day and RR 1.18 at 2,000 mg/day; the hospitalisation cost of AF events attributable to supplementation is subtracted from gross savings to avoid overstating net benefit. No material adverse event offsets are applied to Phytosterols or Beta-Glucan at the modelled doses, consistent with the safety profiles confirmed by EFSA.

Under the final model, all 28 EU27+UK geographies record positive net benefit across all three base-case interventions, reflecting the use of total societal CVD cost per incident case as the unit cost basis. The ratio of supplementation cost to gross HCCS is 0.114 for Omega-3, 0.111 for Phytosterols, and 0.206 for Beta-

Glucan at EU27+UK aggregate level in 2025, meaning supplement expenditure represents between 11% and 21% of the healthcare cost savings generated in every national market. The geographic distribution of net benefit and the country-level drivers of variation in the HCCS-to-supplement-cost ratio are examined in detail in Section 7.5.

7.2 Avoided CVD Events

7.2.1 Methodology for event avoidance estimation

Avoided cardiovascular events are estimated through a three-stage process applied to each country and each year across the projection window. In the first stage, the baseline MACE event rate is established for the eligible population using country-level incident MACE case data from the CVD burden epidemiology dataset, expressed as an event rate per eligible person. In the second stage, the absolute risk reduction for each intervention is applied to this baseline rate to yield the ARR, the reduction in event probability per person per year attributable to supplementation. In the third stage, avoidable events are calculated as the product of the ARR and the eligible population denominator, giving the total number of incident MACE cases that could be avoided annually in each country under full population coverage.

The ARR is derived from the intervention-specific efficacy parameters described in Section 7.1.2 and embedded in the source epidemiological model. For Omega-3, the ARR reflects the RRR of 5% at the base-case dose of 1g/day, rising to 9% at the enhanced dose of 2g/day, applied to the baseline MACE incidence rate in the high triglycerides eligible population. For Phytosterols and Beta-Glucan, the ARR reflects the LDL-C reduction translated to a cardiovascular event RRR via the Gould et al. (2007) / Ference et al. (2012, 2017) risk translation coefficient, 7% at 1.5g/day rising to 12% at 3g/day for Phytosterols, and 6.4% at 3g/day for Beta-Glucan, applied to the baseline MACE incidence rate in the high total cholesterol eligible population. NNT is calculated as the reciprocal of ARR and expresses the number of individuals who must supplement for one year to avoid one MACE event. NNT varies across countries in proportion to underlying MACE incidence. This is a feature of the methodology rather than an artefact and reflects differences in baseline cardiovascular event risk across geographies. Countries with higher baseline MACE incidence generate a higher ARR at the same intervention-specific RRR and therefore a lower NNT. Country-level NNT results for each intervention are presented in Section 7.2.2.

7.2.2 Avoided Event Results, Base Case (1,000 mg/day Omega-3; 1,500 mg/day Phytosterols; 3,000 mg/day Beta-Glucan), 2025

At the 2025 base year, the EU27+UK aggregate avoidable incident MACE events under the base-case dose scenario are estimated at approximately 0.644 million per year for Omega-3 EPA+DHA at a 5% MACE RRR, 2.193 million per year for Phytosterols at a 7% MACE RRR derived from an LDL-C reduction of 0.30 mmol/L via the Gould et al. (2007) / Ference et al. (2012, 2017) risk translation framework, and 2.005 million per year for Beta-Glucan at a 6.4% MACE RRR derived from an LDL-C reduction of 0.29 mmol/L. These estimates reflect the application of each intervention's base-case ARR, the product of the ER baseline incidence rate and the intervention-specific RRR, to the eligible 55-plus population in each of the 28 EU27+UK

geographies. The combined base-case total across all three interventions reaches approximately 4.842 million avoidable incident MACE events per year at the 2025 base year.

Country-level results show the largest absolute avoided event volumes in Germany, Italy, France, the UK, and Spain, reflecting the combined effect of large eligible populations and high baseline MACE incidence rates in the 55-plus population. NNT ranges from approximately 44 in France to 69 in Malta for Omega-3 at 1,000 mg/day, and from 31 in France to 49 in Malta for Phytosterols at 1,500 mg/day, and from 34 in France to 54 in Malta for Beta-Glucan at 3,000 mg/day, across the 28 EU27+UK geographies. This variation is the expected result of the model structure: NNT is the reciprocal of ARR, and ARR is the product of the ER baseline incidence rate and the RRR. Countries with higher baseline MACE incidence generate higher ARR at the same RRR, and therefore lower NNT. The intervention is not more clinically effective in lower-NNT countries, the RRR is fixed at 5%, 7%, and 6.4% respectively regardless of geography, but the absolute return per supplement user is greater where the underlying disease burden is higher.

At current retail supplement prices, supplementation costs represent approximately 11% of gross HCCS for Omega-3 and Phytosterols and approximately 21% for Beta-Glucan across the EU27+UK, meaning all three interventions generate substantial positive net benefit in every geography under the base-case scenario. The economic value of each avoided incident MACE event, measured as the total societal CVD cost per incident case derived from Luengo-Fernández et al. (2023) inflated to 2025 euros and divided by country-level MACE incidence, substantially exceeds supplementation expenditure in all 28 countries at current retail prices. The geographic distribution of net benefit and its country-level drivers are examined in detail in Section 7.5.

7.2.3 Avoided Event Results, Enhanced Scenario (2,000 mg/day Omega-3; 3,000 mg/day Phytosterols), 2025

Under the enhanced dose scenario, the RRR for Omega-3 increases from 5% to 9%, consistent with the Yan et al. 2024 dose-response meta-regression finding of a 5% MACE RRR per additional 1 g/day of EPA+DHA applied to the incremental gram from 1,000 mg/day to 2,000 mg/day, and the LDL-C reduction for Phytosterols increases from approximately 0.30 mmol/L to 0.54 mmol/L at 3,000 mg/day, equivalent to a 12% MACE RRR via the Gould et al. (2007) / Ference et al. (2012, 2017) framework, compared with 7% at the base-case dose. Beta-Glucan is not modelled under an enhanced dose scenario given the absence of an EU-authorised higher-dose health claim and the limited evidence base above 3 g/day in the EU population context.

The higher RRR and LDL-C reduction values at the enhanced dose produce proportionally higher ARR values and correspondingly lower NNT across all 28 countries. EU27+UK aggregate avoidable events under the enhanced scenario reach approximately 2.804 million per year for Omega-3 at 2,000 mg/day, an 80% increase over the 0.644 million base-case figure, and approximately 9.111 million per year for Phytosterols at 3,000 mg/day, a 71% increase over the 2.193 million base-case figure. NNT falls from a range of approximately 44 to 69 at the base-case dose to approximately 24 to 38 for Omega-3 at 2,000 mg/day, and from approximately 31 to 49 at the base-case dose to approximately 18 to 29 for Phytosterols at 3,000 mg/day, reflecting greater supplementation efficiency per user at the higher dose.

Supplementation costs increase proportionally with dose. The EU27+UK mean annual cost per user for Omega-3 at 2,000 mg/day is approximately twice the 1,000 mg/day base-case price, and for Phytosterols

the 3,000 mg/day price is approximately twice the 1,500 mg/day price, consistent with dose-proportional retail pricing. Total supplementation cost rises from €4.2 billion to €8.3 billion for Omega-3 and from €14.1 billion to €28.2 billion for Phytosterols at EU27+UK aggregate level. In both cases, gross societal cost savings increase substantially at the enhanced dose, from €36.6 billion to €65.9 billion for Omega-3 and from €127.1 billion to €217.9 billion for Phytosterols, resulting in a higher absolute net benefit relative to the base case. The enhanced dose scenarios therefore generate greater absolute clinical and economic benefits where the higher dose is clinically appropriate.

The relative economics of dose escalation differ between interventions. The relative economics of dose escalation are similar for both interventions. For Phytosterols, the LDL-C reduction increases from 0.30 mmol/L at 1,500 mg/day to 0.54 mmol/L at 3,000 mg/day, representing an 80% increase in efficacy for a 100% increase in dose and price. For Omega-3, the RRR increases from 5% to 9%, also representing an 80% efficacy gain for a 100% increase in dose and price at 2,000 mg/day. Despite efficacy increasing less than proportionally to dose, the higher efficacy results in greater absolute net benefit at the enhanced dose for both interventions. For Omega-3, net benefit increases from €32.5 billion to €57.6 billion. The enhanced-dose scenarios therefore generate greater absolute clinical and economic benefits where the higher dose is clinically appropriate, with the caveat that the Omega-3 enhanced scenario is anchored on a conservative interpretation of the dose-response evidence at food supplement doses rather than high-dose pharmaceutical preparations.

7.2.4 Forecast to 2035

Annual avoided event estimates are projected forward from 2025 to 2035 using Eurostat demographic projections applied to the eligible population denominator and stable risk factor prevalence assumptions.

Over the projection window, the eligible population remains broadly stable across the EU27+UK, as demographic ageing in some countries is largely offset by population contraction in others. The net effect is a near-stable avoidable event total, with EU27+UK aggregate avoidable events under the base-case scenario reaching approximately 0.644 million for Omega-3, 2.200 million for Phytosterols, and 2.011 million for Beta-Glucan by 2035.

The net effect is a broadly stable avoidable event total across the projection window, with EU27+UK aggregate avoidable events under the base-case scenario reaching approximately 0.644 million for Omega-3, 2.200 million for Phytosterols, and 2.011 million for Beta-Glucan by 2035, reflecting the near-stability of the eligible population denominators documented in Section 3.4.

The table below presents the annual progression of total societal CVD cost, combined gross societal cost savings, and combined net benefit across the 2025–2035 projection window.

Year	Total societal CVD cost	Combined gross HCCS	Combined net benefit
2025	307.3	279.9	237.8
2026	315.5	285.8	242.9
2027	323.9	293.3	249.5
2028	332.5	301.1	256.2
2029	341.3	309.0	263.1
2030	350.3	317.1	270.2
2031	359.5	325.4	277.5
2032	369	333.9	285.0
2033	378.7	342.7	292.6
2034	388.7	351.6	300.5
2035	398.9	360.8	308.5

Table 7.2 - Annual progression in EU27+UK combined base-case results in billion euros

The chart below illustrates the widening economic case for food supplement intervention across the 2025–2035 projection window. Total societal CVD cost rises from €307 billion to €399 billion, driven by demographic ageing and healthcare cost inflation. Combined gross societal cost savings reach €361 billion by 2035, reflecting the relationship between CVD burden and supplementation-generated savings under full eligible population coverage. Combined net benefit grows from €238 billion to €309 billion, demonstrating that the positive net benefit is not a static finding but strengthens over the projection period as societal CVD costs rise.

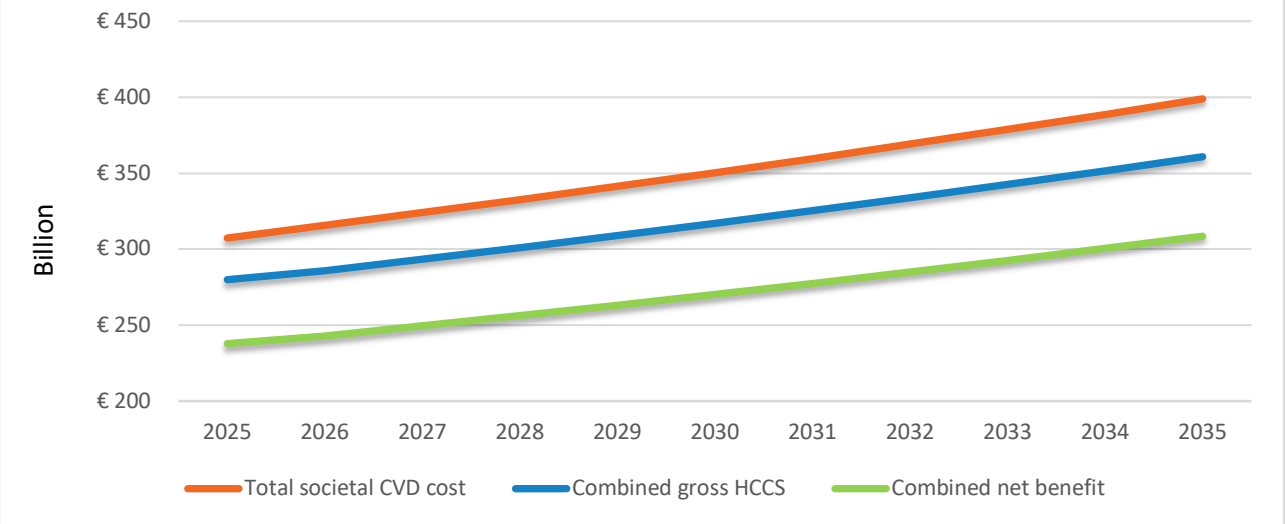

Figure 7.2 - Annual progression in EU27+UK combined base-case results Healthcare Cost Savings (S)

7.2.5 Direct hospitalisation cost savings

Direct healthcare and social care cost savings are derived by applying the country-level H&SC cost per incident MACE case to the volume of avoided events estimated in Section 7.2.

The H&SC cost per incident case varies substantially across EU27+UK, from approximately €7,964 per case in Latvia to €56,638 in Ireland, reflecting differences in hospital tariff structures, length of stay norms, post-acute care intensity, and healthcare system unit costs. These country-level unit costs are sourced from Luengo-Fernández et al. (2023), inflated from the 2021 base year to 2025 euros at the country-level healthcare cost CAGR, and cross-validated against EHN economic burden data and WHO-CHOICE hospital cost benchmarks.

The H&SC component represents the largest single cost category in most countries but its share of total societal cost per incident MACE case varies considerably across geographies. At the EU27+UK unweighted mean, H&SC costs account for approximately 51% of the full societal cost per incident case, ranging from 34% in Latvia to 66% in the Netherlands. In higher-burden Eastern European countries such as Croatia, Latvia, Lithuania, and Romania, the H&SC share is lower, between 34% and 42%, reflecting relatively compressed hospital tariff structures combined with substantial informal care burdens that fall on family members rather than the formal health system. In Northern and Western European countries with higher per-case H&SC expenditure and more developed community rehabilitation infrastructure, the informal care and productivity components represent a proportionally smaller but still material share of the total.

The total societal cost per incident MACE case ranges from €26,019 in Bulgaria to €110,990 in Ireland, a 4.3-fold differential that drives the geographic variation in gross societal cost savings per avoided event across the model.

Countries with the highest total societal cost per incident case generate the largest gross societal cost savings per avoided event and therefore the most favourable economics relative to supplementation expenditure.

Countries at the lower end of the cost distribution, including Bulgaria, Croatia, Romania, and Latvia, generate more modest gross societal cost savings per avoided event despite often having higher avoidable event volumes, reflecting the interaction between high disease burden and relatively lower unit costs that characterises lower-income health systems across the EU27+UK.

For the O3 base-case scenario at EU27+UK aggregate level in 2025, direct H&SC savings account for €19.9 billion of the €36.6 billion gross societal cost savings, with the remaining €16.7 billion split between informal care and productivity components. The H&SC share is stable across interventions given that all three use the same country-level cost-per-case structure; the absolute magnitude differs only in proportion to the volume of avoided events.

7.2.6 Productivity gains from avoided premature cardiovascular death

Productivity savings capture the productivity-loss component of the societal economic burden associated with incident cardiovascular events. In the model, this component is derived from the country-level CVD

cost structure reported by Luengo-Fernández et al. (2023), rather than through a separate valuation of avoided premature deaths based on GDP per capita, remaining working life, or employment rates.

For each country, the productivity-loss share of total CVD costs reported in the source dataset is applied to the projected total CVD cost. The resulting annual productivity cost is divided by the number of incident MACE cases to derive a country-specific productivity cost per incident case. This per-case value is then applied to the estimated number of avoidable MACE events for each intervention and scenario.

Differences in productivity savings across EU27+UK countries therefore reflect both the country-specific share of CVD costs attributable to productivity losses and the number of avoidable cardiovascular events generated by the model. Productivity savings form one component of the full societal cost perspective, alongside direct health and social care costs and informal care costs, with all three components summing to the total societal cost savings associated with avoided incident MACE events.

7.2.7 Informal care cost savings

Informal care savings capture the reduction in unpaid care provided by family members and other informal caregivers associated with avoided incident cardiovascular events. In the model, informal care costs are derived from the country-level CVD cost structure reported by Luengo-Fernández et al. (2023).

For each country, the informal care share of total CVD costs is applied to the projected total societal CVD cost. The resulting annual informal care cost is divided by the number of incident MACE cases to derive a country- and year-specific informal care cost per incident case. This value is then applied to the estimated number of avoidable MACE events for each intervention and scenario.

Informal care represents a material component of the societal burden of CVD, particularly in countries where a greater proportion of care is provided outside formal health and social care systems. Informal care savings are therefore included alongside direct H&SC savings and productivity gains in the full societal cost-savings perspective used throughout the model.

7.2.8 Total societal care cost savings (S)

Total societal cost savings are the sum of direct H&SC savings, informal care savings, and productivity gains, expressed as the total societal CVD cost per incident case multiplied by the volume of avoided events in each country and year. This is the primary cost-savings metric used throughout the model, consistent with the full societal perspective adopted in Section 7.1.4. The breakdown of total societal cost savings by cost component, H&SC, informal care, and productivity, is available in the model outputs for each country and year, enabling disaggregated analysis for payers or policymakers operating within specific cost perspectives.

At the 2025 base year, EU27+UK aggregate gross societal cost savings under the base-case dose scenario total €36.6 billion for Omega-3 at 1,000 mg/day, €127.1 billion for Phytosterols at 1,500 mg/day, and €116.2 billion for Beta-Glucan at 3,000 mg/day. Under the enhanced dose scenarios, gross societal cost savings increase to €65.9 billion for Omega-3 at 2,000 mg/day and €217.9 billion for Phytosterols at 3,000 mg/day, reflecting the increase in avoidable events at the higher RRR. Gross societal cost savings increase

steadily across the projection window, reaching €47.4 billion for Omega-3, €163.7 billion for Phytosterols, and €149.7 billion for Beta-Glucan by 2035.

Country	Year	O3 1g Annual Cost/User (€)	O3 1g Gross Societal Savings (M€)	O3 1g Net Benefit (M€)	O3 2g Annual Cost/User (€)	O3 2g Gross Societal Savings (M€)	O3 2g Net Benefit (M€)
Austria	2025	131.25	1,008.61	920.20	262.49	1,815.49	1,638.68
Belgium	2025	132.90	827.42	729.73	265.80	1,489.36	1,293.98
Bulgaria	2025	93.53	314.17	259.83	187.05	565.50	456.83
Croatia	2025	105.08	137.67	102.99	210.16	247.80	178.45
Cyprus	2025	119.62	49.60	41.78	239.24	89.27	73.65
Czechia	2025	115.18	754.78	657.39	230.36	1,358.61	1,163.82
Denmark	2025	139.38	469.51	421.60	278.76	845.12	749.30
Estonia	2025	106.67	78.03	68.22	213.35	140.45	120.83
Finland	2025	123.77	545.30	498.37	247.53	981.54	887.67
France	2025	120.90	5,350.40	4,939.61	241.79	9,630.72	8,809.14
Germany	2025	133.61	9,278.52	8,405.80	267.22	16,701.34	14,955.89
Greece	2025	97.85	570.56	485.07	195.70	1,027.00	856.03
Hungary	2025	103.46	493.45	414.44	206.92	888.20	730.18
Ireland	2025	193.48	405.51	358.83	386.97	729.91	636.56
Italy	2025	120.16	4,064.86	3,536.08	240.32	7,316.75	6,259.19
Latvia	2025	98.90	68.41	53.19	197.80	123.13	92.69
Lithuania	2025	111.19	205.78	179.78	222.37	370.40	318.40
Luxembourg	2025	209.04	53.48	46.15	418.07	96.27	81.61
Malta	2025	127.65	25.12	20.48	255.29	45.22	35.94
Netherlands	2025	142.47	1,267.42	1,122.78	284.94	2,281.35	1,992.08
Poland	2025	104.47	2,128.55	1,849.72	208.94	3,831.40	3,273.72
Portugal	2025	107.67	465.08	381.13	215.34	837.14	669.25
Romania	2025	102.84	793.07	638.73	205.68	1,427.53	1,118.85
Slovakia	2025	102.43	253.87	216.41	204.86	456.97	382.05
Slovenia	2025	115.36	137.56	119.30	230.72	247.60	211.09
Spain	2025	114.81	2,954.16	2,618.67	229.61	5,317.50	4,646.50
Sweden	2025	128.93	769.72	696.93	257.85	1,385.50	1,239.91
UK	2025	120.71	3,145.32	2,673.15	241.41	5,661.58	4,717.24
EU27	2025	**122.32**	**33,470.59**	**29,783.20**	**244.64**	**60,247.07**	**52,872.29**
EU27+UK	2025	**122.26**	**36,615.92**	**32,456.36**	**244.52**	**65,908.65**	**57,589.53**

Table 7.2.8.1 - Country-Level Omega-3 Supplement Costs, Gross Societal Cost Savings and Net Benefits, Base and Enhanced Dose Scenarios, 2025

Note: O3 = Omega-3 EPA+DHA; H&SC = health and social care. Gross societal cost savings include direct H&SC savings, informal care savings, and productivity gains. Net benefit is calculated as gross societal cost savings minus total supplementation costs. The 1 g/day scenario represents the base case and the 2 g/day scenario the enhanced-dose scenario. Monetary values are expressed in € million unless otherwise stated.

Country	Year	PS 1.5g Annual Cost/User (€)	PS 1.5g Gross Societal Cost Savings (M€)	PS 1.5g Net Benefit (M€)	PS 3g Annual Cost/User (€)	PS 3g Gross Societal Cost Savings (M€)	PS 3g Net Benefit (M€)
Austria	2025	182.26	3,356.61	3,064.77	364.52	5,754.19	5,170.51
Belgium	2025	184.56	2,882.17	2,544.63	369.11	4,940.86	4,265.79
Bulgaria	2025	129.87	812.57	673.18	259.75	1,392.97	1,114.19
Croatia	2025	145.92	406.79	305.15	291.85	697.35	494.07
Cyprus	2025	166.11	150.70	127.16	332.21	258.35	211.26
Czechia	2025	159.94	2,480.40	2,162.92	319.89	4,252.11	3,617.16
Denmark	2025	193.56	1,849.97	1,662.73	387.12	3,171.37	2,796.89
Estonia	2025	148.14	274.93	240.63	296.28	471.30	402.71
Finland	2025	171.87	2,166.02	1,981.09	343.74	3,713.18	3,343.32
France	2025	167.87	21,033.39	19,431.66	335.75	36,057.25	32,853.77
Germany	2025	185.54	31,995.43	29,010.30	371.08	54,849.31	48,879.05
Greece	2025	135.87	1,640.36	1,396.58	271.75	2,812.04	2,324.49
Hungary	2025	143.66	1,426.01	1,199.54	287.32	2,444.59	1,991.66
Ireland	2025	268.69	1,503.80	1,332.11	537.38	2,577.95	2,234.56
Italy	2025	166.86	13,539.59	11,792.57	333.73	23,210.73	19,716.68
Latvia	2025	137.35	209.04	162.91	274.69	358.36	266.09
Lithuania	2025	154.40	615.85	538.68	308.80	1,055.75	901.40
Luxembourg	2025	290.29	188.97	163.28	580.57	323.95	272.56
Malta	2025	177.27	77.73	63.50	354.54	133.26	104.79
Netherlands	2025	197.85	4,824.92	4,278.76	395.71	8,271.30	7,178.97
Poland	2025	145.07	6,474.63	5,633.34	290.14	11,099.36	9,416.79
Portugal	2025	149.51	1,534.79	1,260.03	299.02	2,631.07	2,081.54
Romania	2025	142.82	2,099.73	1,694.37	285.64	3,599.54	2,788.82
Slovakia	2025	142.25	821.05	700.87	284.50	1,407.51	1,167.15
Slovenia	2025	160.20	452.07	392.56	320.40	774.98	655.95
Spain	2025	159.42	10,224.69	9,072.91	318.85	17,528.04	15,224.48
Sweden	2025	179.03	3,116.08	2,823.77	358.06	5,341.85	4,757.23
UK	2025	167.62	10,946.91	9,316.89	335.24	18,766.13	15,506.08
EU27	2025	**169.86**	**116,158.29**	**103,710.00**	**339.72**	**199,128.50**	**174,231.91**
EU27+UK	2025	**169.78**	**127,105.20**	**113,026.88**	**339.56**	**217,894.64**	**189,738.00**

Table 7.2.8.2 - Country-Level Phytosterol Supplement Costs, Gross Societal Cost Savings and Net Benefits, Base and Enhanced Dose Scenarios, 2025

Note: PS = Phytosterols. The 1.5 g/day scenario represents the base case and the 3 g/day scenario the enhanced-dose scenario. Gross societal cost savings comprise H&SC, informal care and productivity savings. Net benefit equals gross societal cost savings less supplementation costs. Monetary values are expressed in € million unless otherwise stated.

Country	Year	BG 3g Annual Cost/User (€)	BG 3g Gross Societal Cost Savings (M€)	BG 3g Net Benefit (M€)
Austria	2025	309.84	3,068.90	2,572.78
Belgium	2025	313.74	2,635.12	2,061.32
Bulgaria	2025	220.80	742.92	505.94
Croatia	2025	248.06	371.92	199.14
Cyprus	2025	282.40	137.79	97.76
Czechia	2025	271.89	2,267.79	1,728.11
Denmark	2025	329.07	1,691.40	1,373.08
Estonia	2025	251.83	251.36	193.06
Finland	2025	292.18	1,980.36	1,665.98
France	2025	285.41	19,230.53	16,507.40
Germany	2025	315.40	29,252.97	24,178.57
Greece	2025	231.00	1,499.75	1,085.32
Hungary	2025	244.23	1,303.78	918.78
Ireland	2025	456.76	1,374.90	1,083.04
Italy	2025	283.68	12,379.06	9,408.98
Latvia	2025	233.49	191.13	112.70
Lithuania	2025	262.47	563.07	431.87
Luxembourg	2025	493.49	172.77	129.09
Malta	2025	301.35	71.07	46.88
Netherlands	2025	336.34	4,411.36	3,482.91
Poland	2025	246.63	5,919.66	4,489.43
Portugal	2025	254.16	1,403.24	936.15
Romania	2025	242.79	1,919.76	1,230.67
Slovakia	2025	241.83	750.67	546.36
Slovenia	2025	272.34	413.32	312.14
Spain	2025	271.03	9,348.29	7,390.17
Sweden	2025	304.38	2,848.98	2,352.02
UK	2025	284.96	10,008.60	7,237.55
EU27	2025	**288.76**	**106,201.87**	**85,039.66**
EU27+UK	2025	**288.63**	**116,210.47**	**92,277.21**

Table 7.2.8.3 - Country-Level Beta-Glucan Supplement Costs, Gross Societal Cost Savings and Net Benefits, Base-Case Scenario, 2025

BG = Beta-Glucan. The 3 g/day scenario represents the base-case dose (RRR 6.4%). Gross societal cost savings comprise direct health and social care (H&SC) savings, informal care savings, and productivity gains associated with avoided MACE events. Net benefit equals gross societal cost savings less total supplementation costs. Monetary values are expressed in € million unless otherwise stated.

7.3 Supplement Costs (C)

7.3.1 Unit cost methodology

Supplement unit costs are expressed as the annual cost of supplementation per eligible user in euros. The 2025 base-year prices represent the primary observed data point for each country and dose scenario: retail prices were collected in 2025 by systematically reviewing leading online supplement platforms active in each of the 28 EU27+UK markets, including national market leaders and pan-European platforms, and selecting the lowest available price for a compliant product at the relevant dose. Prices are collected at the standard therapeutic dose, 1,000 mg/day and 2,000 mg/day for Omega-3 EPA+DHA, 1,500 mg/day and 3,000 mg/day for Phytosterols, and 3,000 mg/day for Beta-Glucan. This lowest-available-price approach provides the most conservative possible supplementation cost baseline: it minimises the supplementation cost input and therefore produces the most favourable attainable net benefit estimate under current market conditions. All prices reflect individual consumer retail costs with no institutional, bulk purchasing, or reimbursement discount applied.

Where direct online price observation was available in a national market, the lowest listed retail price for a compliant product at the relevant dose was recorded. Ten countries had sufficient e-commerce infrastructure to yield reliable direct observations: Austria, Belgium, Denmark, Finland, Germany, Ireland, Luxembourg, Malta, the Netherlands, and Sweden. For the remaining 18 countries, Bulgaria, Croatia, Cyprus, Czechia, Estonia, France, Greece, Hungary, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and the UK, prices were extrapolated by applying Eurostat COICOP purchasing power parity indices for food supplements relative to Austria as the reference market. Austria was selected as the reference given its central position in the EU price distribution and the availability of a robust observed price across all five dose scenarios. The PPP-adjusted extrapolation multiplier is applied uniformly across all supplement types and dose scenarios for a given country, meaning the cross-country price relativities are identical across Omega-3, Phytosterols, and Beta-Glucan within the extrapolated markets. This approach is consistent with the assumption that cross-national price variation in the nutraceutical retail segment is driven primarily by general consumer price level differentials rather than supplement-category-specific market dynamics. PPP indices for extrapolated countries range from 0.69 relative to Austria in Bulgaria to 0.89 in France.

At the 2025 base year, the EU27+UK range of annual supplement costs per user is €94 to €209 for Omega-3 at 1g/day, €187 to €418 for Omega-3 at 2g/day, €130 to €290 for Phytosterols at 1.5g/day, €260 to €581 for Phytosterols at 3g/day, and €221 to €493 for Beta-Glucan at 3g/day. Bulgaria records the lowest national price and Luxembourg the highest across all five scenarios. Eastern European countries, Bulgaria, Greece, Latvia, Slovakia, Romania, Hungary, Croatia, and Poland, consistently occupy the bottom of the price distribution, while Luxembourg, Ireland, the Netherlands, and Denmark anchor the upper end.

The EU27+UK unweighted mean annual cost per user in 2025 is €122 for Omega-3 at 1g/day, €245 for Omega-3 at 2g/day, €170 for Phytosterols at 1.5g/day, €340 for Phytosterols at 3g/day, and €289 for Beta-Glucan at 3g/day. Expressed on a per-gram basis, the mean cost is €0.33 per gram for Omega-3 at both the base-case and enhanced doses, confirming dose-proportional retail pricing with no non-linear concentration premium at the 2g/day level. Phytosterols exhibit an identical per-gram price of €0.31 at

both 1.5g/day and 3g/day, consistent with dose-proportional retail pricing where a doubled quantity yields a doubled annual cost. Industry assessment suggests a typical EU market average of approximately €0.26/g for phytosterols, marginally below the model's base-case assumption; the base-case figure is therefore conservative, and net benefit estimates for PS 1.5g/day and PS 3g/day may be modestly understated relative to typical market pricing. The delivery format context and pricing rationale for phytosterols are discussed further in Section 5.1. Beta-Glucan at 3g/day carries the lowest per-gram cost of the three interventions at €0.26, though its high daily dose means it generates the highest annual supplementation cost in absolute terms for the PS/BG eligible population at current EU mean pricing.

From the 2025 base year, supplement prices are projected forward across the 2026–2035 window using country-specific annual growth rates derived from PPP-adjusted GDP per capita data (World Bank World Development Indicators, 2024 release). Countries with higher per capita income are assigned a 2.00% per annum floor rate, reflecting the relatively stable consumer price environment for food supplements in mature, higher-income markets. This floor is consistent with the EU harmonised index of consumer prices (HICP) average annual increase for food products over the 2015–2023 period and is applied as a conservative lower bound for supplement price inflation in mature markets. Countries with lower per capita income are assigned modestly higher growth rates, reflecting faster convergence of supplement retail prices toward EU norms as consumer purchasing power and market penetration increase. The ten highest-income markets, Austria, Belgium, Denmark, Finland, Germany, Ireland, Luxembourg, Malta, the Netherlands, and Sweden, are all assigned the 2.00% floor. The remaining 18 countries are assigned rates ranging from 2.06% in France and 2.07% in the UK to 2.74% in Bulgaria.

The same country-specific CAGR is applied uniformly across Omega-3, Phytosterols, and Beta-Glucan within each country, on the basis that retail price inflation in the food supplement category is driven by country-level macroeconomic conditions rather than ingredient-specific supply dynamics. The EU27+UK population-weighted mean CAGR across the projection window is 2.22%.

It should be noted that the lowest-available-price methodology applied to Omega-3 EPA+DHA may understate the typical market cost faced by consumers. Industry assessment indicates that lower-priced qualifying products frequently deliver only 150–200 mg EPA+DHA per capsule, such that achieving 1,000 mg/day of combined EPA+DHA requires six or more capsules daily. A more realistic single-product retail price for a supplement delivering 1,000 mg EPA+DHA/day in a typical capsule count is approximately €1/day, or €365/year, compared to the EU27+UK population-weighted mean base-case price of €120/year. The economic implications of this higher price point are examined in the sensitivity analysis as Parameter 6 in Section 7.6. The higher supplementation cost provides a more conservative test of the economic case for Omega-3 at 1 g/day than the lowest-available-price assumption used in the base case.

7.3.2 Total supplement costs by scenario

Total supplementation cost is the product of the annual per-user supplement price and the eligible population in each country and year, summed across all 28 EU27+UK geographies. It represents the aggregate retail expenditure that would be required to supplement the full eligible population at each dose scenario and is the primary cost input to the net benefit calculation.

At the 2025 base year, EU27+UK aggregate annual supplementation costs under full eligible population coverage are €4.2 billion for Omega-3 at 1g/day, €8.3 billion for Omega-3 at 2g/day, €14.2 billion for Phytosterols at 1.5g/day, €28.3 billion for Phytosterols at 3g/day, and €24.1 billion for Beta-Glucan at 3g/day. The combined base-case supplementation cost across all three interventions, Omega-3 at 1g/day, Phytosterols at 1.5g/day, and Beta-Glucan at 3g/day, totals €42.4 billion per year in 2025. The corresponding enhanced scenario total, substituting the 2g/day Omega-3 and 3g/day Phytosterols doses, reaches €60.8 billion per year, a 43% increase over the base case driven by the doubling of per-user Omega-3 and Phytosterols costs at the enhanced dose.

In all five scenarios, Phytosterols and Beta-Glucan generate substantially higher total supplementation costs than Omega-3, despite similar per-gram prices, because their eligible population, the 83.7 million adults aged 55 and above with elevated total cholesterol or familial hypercholesterolaemia, is 2.4 times larger than the Omega-3 eligible population of 34.6 million adults with elevated triglycerides. Beta-Glucan generates a higher total supplementation cost than Phytosterols at the base-case dose because both interventions are applied to the same 83.7 million eligible population, while the population-weighted mean annual cost per user is higher for Beta-Glucan at 3 g/day (€286) than for Phytosterols at 1.5 g/day (€168). The population-weighted mean annual cost per user in 2025 is €120 for Omega-3 at 1g/day, €240 for Omega-3 at 2g/day, €168 for Phytosterols at 1.5g/day, €336 for Phytosterols at 3g/day, and €286 for Beta-Glucan at 3g/day.

A critical structural feature of the model is that in every scenario supplementation costs represent a relatively small fraction of gross societal cost savings. The ratio of supplementation cost to gross societal cost savings in 2025 is 0.114 for Omega-3 at 1 g/day, 0.126 for Omega-3 at 2 g/day, 0.111 for Phytosterols at 1.5 g/day, 0.129 for Phytosterols at 3 g/day, and 0.206 for Beta-Glucan at 3 g/day, meaning supplement expenditure represents approximately 11% to 21% of the gross societal cost savings generated across the five scenarios. This structure means that net benefit is positive across all scenarios and all 28 geographies at current retail prices.

Over the 2025–2035 projection window, annual base-case supplementation costs grow from €42.4 billion in 2025 to €52.6 billion in 2035, driven primarily by the country-specific supplement price CAGRs of 2.00% to 2.74%, while the aggregate eligible populations remain broadly stable across the projection window. Gross societal cost savings also increase over the period as the projected societal cost per incident cardiovascular event rises. Since gross societal cost savings substantially exceed supplementation costs in every year and every scenario, net benefit remains strongly positive and increases across the projection window.

7.3.3 Supplement Price Projection Methodology

Base-year supplement prices were established for 2025 through systematic retail price surveys across the leading online supplement platforms active in each of the 28 EU27+UK markets, selecting the lowest available compliant product price at each dose scenario. Ten markets with sufficient e-commerce infrastructure, Austria, Belgium, Denmark, Finland, Germany, Ireland, Luxembourg, Malta, the Netherlands, and Sweden, yielded direct price observations. Austria was selected as the reference market given its central position in the EU price distribution.

For the remaining 18 markets, 2025 prices were derived by applying Eurostat COICOP purchasing power parity indices for food supplements relative to Austria. PPP adjustment translates the Austrian observed price into a comparable local-currency equivalent for each country, reflecting national differences in consumer purchasing power and retail market conditions rather than applying a uniform EU average. PPP indices for extrapolated markets range from 0.69 in Bulgaria to 0.89 in France relative to Austria, meaning that a supplement retailing at €200 per year in Austria would be priced at approximately €138 in Bulgaria and €178 in France under the PPP-adjusted methodology.

From the 2025 base year, prices are projected forward to 2035 using country-specific annual growth rates derived from PPP-adjusted GDP per capita. The ten highest-income markets are assigned a 2.00% per annum floor rate, consistent with the stable consumer price environment for food supplements in mature markets. The remaining 18 countries are assigned rates ranging from 2.06% to 2.74%, reflecting faster convergence of supplement retail prices toward EU norms as purchasing power increases. The same country-specific CAGR is applied uniformly across all three ingredients within each country, on the basis that retail price inflation in the food supplement category is driven by country-level macroeconomic conditions rather than ingredient-specific supply dynamics. The EU27+UK population-weighted mean CAGR across the projection window is 2.22%.

7.3.4 Geographic Distribution of Supplement Costs and Affordability

This geographic price gradient interacts with the societal cost per incident MACE case and therefore influences the economic return generated by supplementation across the EU27+UK. In markets where societal CVD costs per incident case are higher, supplementation expenditure generally represents a smaller proportion of the gross societal cost savings generated. Conversely, countries with lower societal costs per incident case can record higher supplementation cost-to-gross-savings ratios despite lower absolute supplement prices. These geographic differences reflect variation in the economic value attributed to avoided cardiovascular events rather than differences in intervention efficacy, as the intervention-specific RRR is held constant across countries.

The geographic results therefore indicate that the economic case for supplementation varies across national markets according to the interaction between supplement prices, eligible population size, baseline cardiovascular event rates, and societal costs per incident event. Nevertheless, net benefit remains positive across all 28 EU27+UK geographies under the modelled base-case scenarios. Policy mechanisms that reduce the cost of supplementation, including taxation, subsidy, reimbursement, or institutional procurement approaches, could further improve the economic return where supplement expenditure represents a larger proportion of the societal savings generated. The appropriate mechanism would depend on country-specific healthcare, fiscal, and regulatory conditions and is not assessed directly within the model.

7.4 Net benefit by country and scenario (B = S – C)

Net economic benefit is the difference between gross societal cost savings (S) and total supplementation cost (C) in each country and year (B = S − C). At the 2025 base year, net benefit is positive across all five

dose scenarios and all 28 EU27+UK geographies, reflecting the consistent finding that the total societal CVD cost per incident case substantially exceeds supplementation expenditure in every national market. EU27+UK aggregate net benefit in 2025 is €32.5 billion for Omega-3 at 1 g/day, €57.6 billion for Omega-3 at 2 g/day, €113.0 billion for Phytosterols at 1.5 g/day, €189.7 billion for Phytosterols at 3 g/day, and €92.3 billion for Beta-Glucan at 3 g/day.

Country-level variation in net benefit reflects the interaction between the societal cost per incident case across geographies, country-specific supplement prices, and the size of the eligible population. For Omega-3 at the base-case dose, the largest absolute net benefit is recorded in Germany (€8.4 billion), France (€4.9 billion), Italy (€3.5 billion), the UK (€2.7 billion), and Spain (€2.6 billion), driven primarily by their large eligible populations. The smallest absolute net benefit is observed in Malta (€20 million), Cyprus (€42 million), Latvia (€53 million), and Estonia (€68 million), reflecting their substantially smaller eligible populations. At EU27+UK aggregate level in 2025, net benefit per avoided incident MACE event is approximately €50,466 for Omega-3, €51,526 for Phytosterols, and €46,058 for Beta-Glucan.

7.4.1 EU27+UK aggregate results

At the 2025 base year, EU27+UK aggregate net benefit across the three base-case interventions totals €32.5 billion for Omega-3 at 1,000 mg/day, €113.0 billion for Phytosterols at 1,500 mg/day, and €92.3 billion for Beta-Glucan at 3,000 mg/day, a combined €237.8 billion. The net benefit per avoided incident MACE event is €50,466 for Omega-3, €51,526 for Phytosterols, and €46,058 for Beta-Glucan. The ratio of supplementation cost to gross societal cost savings is 0.114 for Omega-3, 0.111 for Phytosterols, and 0.206 for Beta-Glucan, with Beta-Glucan recording the highest ratio because of its higher supplementation cost relative to the gross societal cost savings generated. Under the enhanced-dose scenarios, net benefit increases to €57.6 billion for Omega-3 at 2,000 mg/day and €189.7 billion for Phytosterols at 3,000 mg/day.

Net benefit grows consistently across the projection window. Under the base-case scenario, annual net benefit increases from €32.5 billion in 2025 to €42.3 billion in 2035 for Omega-3, from €113.0 billion to €146.2 billion for Phytosterols, and from €92.3 billion to €120.0 billion for Beta-Glucan. This increase reflects the evolution of societal CVD costs and supplementation costs across the projection period.

Over the full 2025–2035 window, cumulative net benefit approximates €408 billion for Omega-3, €1,416 billion for Phytosterols, and €1,159 billion for Beta-Glucan, a combined €2,984 billion across the three base-case interventions. Enhanced-dose scenarios generate greater annual net benefit than their respective base-case scenarios across the projection period. The sensitivity of these results to key modelling assumptions is examined in Section 7.6.

7.4.2 Geographic distribution of net benefit

The geographic distribution of net benefit across the EU27+UK reflects two primary drivers: the absolute size of the eligible population, which determines the scale of both gross societal cost savings and supplementation costs, and the country-level supplementation cost-to-gross-societal-savings ratio, which measures supplementation expenditure relative to the societal cost savings generated. These two drivers

produce a consistent pattern in which the largest absolute net benefits are concentrated in the most populous Western European markets, while the most favourable cost-to-savings ratios are observed in a mixed group of higher-income countries where elevated societal costs per incident MACE event generate proportionally larger gross savings relative to supplement expenditure.

For Omega-3 at the base-case dose, the most favourable cost-to-savings ratios are observed in France (7.7%), Finland (8.6%), Austria (8.8%), Germany (9.4%), and Sweden (9.5%). The least favourable ratios are observed in Croatia (25.2%), Latvia (22.2%), Romania (19.5%), Malta (18.5%), and Portugal (18.0%). All remain below 100%, indicating positive net benefit in every market.

In absolute net benefit terms, the rankings reflect population size: Germany (€8.4 billion), France (€4.9 billion), Italy (€3.5 billion), the UK (€2.7 billion), and Spain (€2.6 billion) account for the largest shares of EU27+UK aggregate net benefit for Omega-3, together representing approximately 66% of the EU27+UK total.

This geographic pattern is consistent across all three interventions. For Beta-Glucan, which records the highest cost-to-savings ratios of the three interventions because of its higher per-user supplementation cost, the least favourable ratios are observed in Croatia (46.5%), Latvia (40.8%), Romania (35.9%), Malta (33.8%), and Portugal (33.3%). Even in these markets, however, the ratio remains below 100%, indicating positive net benefit for Beta-Glucan at current retail prices.

The geographic consistency of positive net benefit across all interventions and markets reflects the relationship between the societal cost per incident MACE event and supplementation expenditure across the modelled geographies.

Figure 7.5 maps the supplementation cost-to-gross-societal-savings ratio across all 28 EU27+UK geographies for each of the five dose scenarios modelled.

- The ratio expresses supplementation expenditure as a share of gross societal cost savings, with lower values indicating that a smaller proportion of the savings generated is absorbed by supplementation expenditure.
- Across the four Omega-3 and Phytosterol scenarios, the ratio ranges from 7.6% to 29.2%. Beta-Glucan at 3 g/day shows a wider range of 14.2% to 46.5%, reflecting its higher per-user supplementation cost relative to the societal savings generated per avoided event. Eastern European countries, notably Croatia, Latvia, Bulgaria, and Romania, generally record higher ratios, reflecting lower societal CVD costs per incident case relative to supplement retail prices. France, Finland, Austria, and Germany record among the lowest ratios.

These geographic differences provide additional context for assessing the potential economics of supplementation across individual national markets.

A notable exception within the higher-income group is Ireland, which records a relatively high cost-to-savings ratio for Omega-3 at 2 g/day despite having the highest societal CVD cost per incident case in the EU27+UK. This reflects the offsetting effect of Ireland's high supplementation cost, with an annual per-user price of €387 for Omega-3 at 2 g/day.

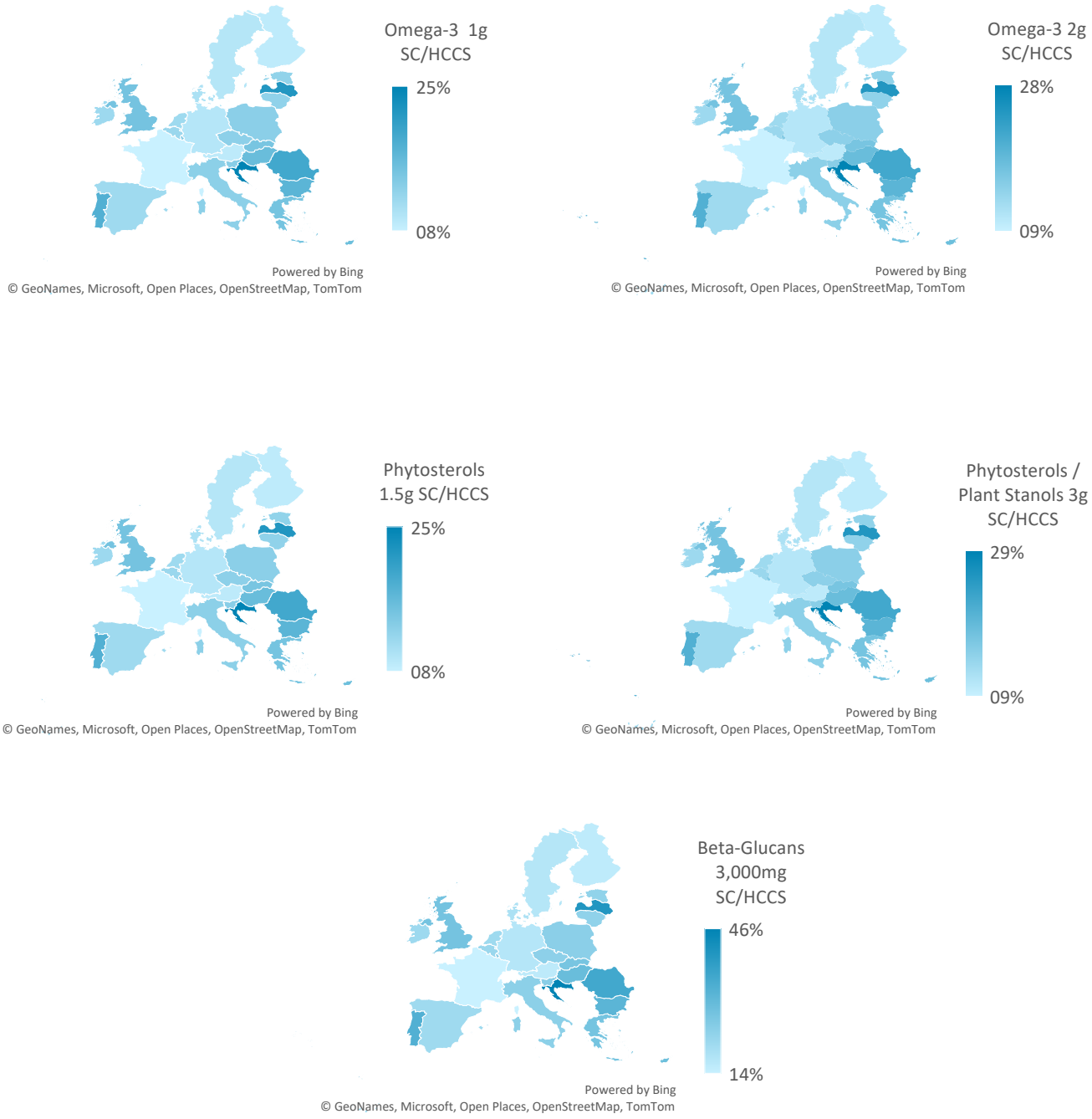

Figure 7.5: Supplementation Cost as a Share of Gross Societal Cost Savings, by Country (2025)

7.5 Sensitivity Analysis

7.5.1 Parameters Tested

Parameter 1, Relative Risk Reduction (RRR)

The sensitivity analysis examines the robustness of the base-case net population benefit estimates to variation in five key parameters. These parameters were selected based on their influence on model outputs and the degree of uncertainty associated with their base-case assumptions. For each parameter, low- and high-bound scenarios are assessed, with results reported for all three interventions at the EU27+UK aggregate level for the 2025 reference year.

Parameter 2, Population coverage

The base case models 100% of the eligible population supplementing, producing a theoretical ceiling estimate. The sensitivity scenario applies 50% coverage to all three interventions simultaneously. Because the model scales linearly with population coverage, the 50% coverage scenario produces exactly half the avoided events, gross societal cost savings, supplementation costs, and net benefit of the 100% coverage scenario. Net benefit per supplemented user therefore remains unchanged across coverage levels.

Parameter 3, Supplement annual cost per user

Supplement costs are PPP-adjusted and CAGR-projected from retail price surveys. The sensitivity scenario applies a ±20% variation to the annual cost per user for all three interventions and all 28 countries simultaneously, reflecting the range of price variation observed within each national market across pharmacy, health food retail, and online channels. Because gross societal cost savings are unaffected by supplement price, the full ±20% variation in supplementation expenditure flows directly through to net benefit. Given that supplementation costs represent approximately 11% to 21% of gross societal cost savings across the three base-case interventions, a ±20% variation in supplement prices produces a comparatively modest change in net benefit.

Parameter 4, Cost perspective (full societal vs H&SC only)

The base case applies a full societal cost perspective encompassing health and social care (H&SC), informal care, and productivity losses, as documented by Luengo-Fernández et al. (2023). The sensitivity scenario applies a narrower direct H&SC cost perspective only, excluding informal care and productivity losses. H&SC costs represent approximately 51% of the full societal cost per incident MACE case at the EU27+UK unweighted mean. Applying the H&SC-only perspective therefore reduces gross societal cost savings by approximately 49% relative to the full societal perspective, while leaving supplementation costs unchanged, producing a more conservative net benefit estimate relevant to health-system budget analyses rather than whole-economy assessments. Net benefit remains positive under the H&SC-only perspective for all three interventions and all 28 geographies.

Parameter 5, Eligible population definition (High TG/Chol 55+ vs combined risk 55+)

The base-case eligible population uses the intervention-specific risk-factor denominator: High Triglycerides 55+ for Omega-3 and High Total Cholesterol 55+, including Familial Hypercholesterolaemia 55+, for Phytosterols and Beta-Glucan, producing EU27+UK eligible populations of 34.6 million and 83.7 million, respectively. The sensitivity scenario substitutes the combined cardiovascular risk population aged 55 and above across all three interventions, aggregating adults with the lipid risk factors and familial hypercholesterolaemia included in the model, producing an EU27+UK population of approximately 117 million. The same intervention-specific base-case RRRs are applied to this broader population, generating an upper-bound estimate of the potential economic impact if supplementation were directed at the broader compound-risk-positive 55+ population rather than the intervention-specific lipid subgroup. The resulting changes in avoidable events, gross societal cost savings, supplementation costs, and net benefit are assessed relative to the base-case eligible-population assumptions.

7.5.2 Sensitivity Results

The sensitivity results for the 2025 reference year at the EU27+UK aggregate level are presented below. All figures are expressed in EUR billions for gross HCCS and net benefit, and in thousands for avoidable events. Base-case figures are included for comparison.

RRR sensitivity, avoidable events in million

Intervention	Low RRR	Base RRR	High RRR	Avoidable events low	Avoidable events base	Avoidable events high
O3 1g/day	3%	5%	7%	0.386	0.644	0.902
O3 2g/day	7%	9%	11%	0.901	1.159	1.417
PS 1.5g/day	5%	7%	9%	1.566	2.193	2.82
PS 3g/day	10%	12%	14%	3.133	3.759	4.386
BG 3g/day	4%	6.4%	7%	1.253	2.005	2.193

Avoidable events scale proportionally with RRR, with the magnitude of variation around the base case determined by the intervention-specific low- and high-RRR assumptions. The largest absolute changes in avoidable events are generally observed in countries with larger eligible populations and higher baseline numbers of avoidable MACE events, as any change in RRR is amplified across a larger population at risk.

RRR sensitivity, net benefit (EUR billion, 2025)

Net benefit grows consistently across the projection window. Under the base-case scenario, annual net benefit increases from €32.5 billion in 2025 to €42.3 billion in 2035 for Omega-3, from €113.0 billion to €146.2 billion for Phytosterols, and from €92.3 billion to €120.0 billion for Beta-Glucan.

This growth reflects the increase in projected societal CVD costs over the period, which outpaces the growth in supplementation costs.

Intervention	NB low RRR	NB base	NB high RRR
O3 1g/day	€17.8 bn	€32.5 bn	€47.1 bn
O3 2g/day	€42.9 bn	€57.6 bn	€72.2 bn
PS 1.5g/day	€76.7 bn	€113.0 bn	€149.3 bn
PS 3g/day	€153.4 bn	€189.7 bn	€226.1 bn
BG 3g/day	€48.7 bn	€92.3 bn	€103.2 bn

Over the full 2025–2035 window, cumulative net benefit approximates €408 billion for Omega-3, €1,416 billion for Phytosterols, and €1,159 billion for Beta-Glucan, a combined €2,984 billion across the three base-case interventions. Enhanced-dose scenarios generate greater annual net benefit than their respective base-case scenarios throughout the projection period, reflecting the additional gross societal cost savings generated by the higher modelled RRRs. The conditions governing the sensitivity of these results to key modelling assumptions are examined in Section 7.6.

Population coverage sensitivity, net benefit (EUR billion, 2025)

Net benefit at 50% coverage is exactly half the 100% coverage case, confirming the linear relationship between population coverage and net benefit. The coverage assumption does not alter the per-user economics, only the aggregate scale of the net benefit. At 50% population coverage, EU27+UK aggregate net benefit remains €16.2 billion for Omega-3, €56.5 billion for Phytosterols, and €46.1 billion for Beta-Glucan.

At 30% population coverage, representing a near-term coverage scenario, EU27+UK aggregate net benefit is €9.7 billion for Omega-3, €33.9 billion for Phytosterols, and €27.7 billion for Beta-Glucan, a combined €71.3 billion annually across the three base-case interventions.

All 30% figures are derived by applying the 30% coverage assumption to the corresponding 100% coverage net benefit, consistent with the linear relationship between population coverage and aggregate economic outcomes in the model.

Intervention	NB 100% coverage	NB 50% coverage	NB 30% coverage
O3 1g/day	€32.5 bn	€16.2 bn	€9.7 bn
O3 2g/day	€57.6 bn	€28.8 bn	€17.3 bn
PS 1.5g/day	€113.0 bn	€56.5 bn	€33.9 bn
PS 3g/day	€189.7 bn	€94.9 bn	€56.9 bn
BG 3g/day	€92.3 bn	€46.1 bn	€27.7 bn

Supplement cost sensitivity, net benefit (EUR billion, 2025)

Supplement cost has a direct effect on net benefit because price variation flows entirely through to net benefit without affecting gross societal cost savings. A 20% increase in supplement cost reduces net benefit by approximately €0.83 billion for Omega-3, €2.83 billion for Phytosterols, and €4.82 billion for Beta-Glucan relative to the base case, equivalent to approximately 2.6%, 2.5%, and 5.2% of their respective base-case net benefits. The relatively low sensitivity of net benefit to supplement price variation reflects the structural dominance of gross societal cost savings over supplementation costs: since supplement expenditure represents approximately 11% to 21% of gross societal cost savings across the three base-case interventions, even a substantial change in retail prices has a comparatively modest effect on net benefit.

Intervention	Base price €/g	NB –20% cost	NB base	NB +20% cost
O3 1 g/day	€ 0.33	€33.3 bn	€32.5 bn	€31.6 bn
O3 2 g/day	€ 0.33	€59.3 bn	€57.6 bn	€55.9 bn
PS 1.5 g/day	€ 0.31	€115.8 bn	€113.0 bn	€110.2 bn
PS 3 g/day	€ 0.31	€195.3 bn	€189.7 bn	€184.1 bn
BG 3 g/day	€ 0.26	€97.1 bn	€92.3 bn	€87.5 bn

The base-case Omega-3 supplement cost assumes the lowest observed qualifying EU retail price of approximately €120/year per user at 1,000 mg EPA+DHA/day. Industry stakeholder assessment indicates a typical market retail price of approximately €365/year for a single product delivering the required dose. This sensitivity scenario therefore models the impact of applying €365/year for Omega-3 at 1 g/day and €730/year at 2 g/day, with all other parameters held at their base-case values.

Under this alternative retail-price assumption, the supplementation cost-to-gross-societal-savings ratio for Omega-3 increases from 0.114 to 0.344 at 1 g/day and from 0.126 to 0.381 at 2 g/day. Net benefit decreases by approximately €8.7 billion for Omega-3 at 1 g/day and €17.4 billion at 2 g/day relative to the base case, equivalent to reductions of approximately 27% and 30%, respectively. Net benefit nevertheless remains positive, indicating that the economic case remains favourable under the higher Omega-3 retail-price assumption.

Cost perspective sensitivity, net benefit (EUR billion, 2025)

Restricting the analysis to the H&SC cost perspective reduces gross societal cost savings by approximately 49% relative to the full societal perspective, producing a more conservative net benefit estimate relevant to health-system budget analyses rather than whole-economy assessments.

Under the H&SC-only perspective, net benefit remains positive across all three base-case interventions and all 28 geographies, at €15.8 billion for Omega-3, €55.6 billion for Phytosterols, and €39.8 billion for Beta-Glucan. The full societal perspective remains the primary perspective for the population-level economic analysis because it captures the broader economic burden of cardiovascular events, including H&SC costs, informal care, and productivity losses.

Intervention	NB full societal	NB H&SC only
O3 1g/day	€32.5 bn	€15.8 bn
O3 2g/day	€57.6 bn	€28.0 bn
PS 1.5g/day	€113.0 bn	€55.6 bn
PS 3g/day	€189.7 bn	€93.2 bn
BG 3g/day	€92.3 bn	€39.8 bn

Eligible population sensitivity, net benefit (EUR billion, 2025)

Substituting the base-case eligible populations, 34.6 million for Omega-3 and 83.7 million for Phytosterols and Beta-Glucan, with the combined cardiovascular risk population aged 55 and above, approximately 117 million for all three interventions, and applying the same base-case RRRs results in estimated avoidable-event totals approximately 3.4 times higher for Omega-3 (2,177k versus 644k) and approximately 1.4 times higher for Phytosterols (3,044k versus 2,193k) and Beta-Glucan (2,783k versus 2,005k).

Intervention	Base eligible population	Expanded eligible population	Multiplier	Avoidable events base
O3 1 g/day	34.6M	117M	3.4×	644k
O3 2 g/day	34.6M	117M	3.4×	1,159k
PS 1.5 g/day	83.7M	117M	1.4×	2,193k
PS 3 g/day	83.7M	117M	1.4×	3,759k
BG 3 g/day	83.7M	117M	1.4×	2,005k

Note: Expanded eligible population = combined cardiovascular risk population aged 55+, aggregating adults with elevated triglycerides, elevated total cholesterol, or familial hypercholesterolaemia. Expanded avoidable-event and net-benefit estimates are approximate and are derived by scaling the corresponding base-case values in proportion to the change in eligible population. Under this proportional-scaling assumption, the supplementation cost-to-gross-societal-savings ratio remains unchanged.

Gross societal cost savings, supplementation costs, and net benefit are assumed to scale proportionally with the expanded eligible population, yielding approximate net benefits of €110 billion for Omega-3, €157 billion for Phytosterols, and €128 billion for Beta-Glucan.

Under this proportional-scaling assumption, the supplementation cost-to-gross-societal-savings ratio remains unchanged because both gross societal cost savings and supplementation costs are scaled using the same population multiplier.

This scenario illustrates the potential increase in the scale of gross societal cost savings and net benefit if supplementation were directed at the broader compound-risk-positive population aged 55 and above rather than the intervention-specific base-case eligible populations.

ER Baseline Sensitivity, EU27+UK, 2025

The ER baseline sensitivity applies a ±10% and ±20% scalar to the country-level IHME GBD CVD incidence proportions used to derive the event-rate baseline. The ER baseline is subject to definitional uncertainty given the difference between the I00–I99 all-cardiovascular aggregate and the narrower clinical MACE endpoint, as

discussed in Section 8.10. Supplementation costs are fixed and do not scale with ER; a ±10% ER shock therefore produces an approximately ±11.8% change in combined net benefit, slightly greater than the proportional change in gross societal cost savings because supplementation costs remain unchanged. At −20% ER, combined net benefit falls from €237.8 billion to €181.8 billion. Net benefit remains positive across all three base-case interventions and all 28 EU27+UK geographies at every ER level tested.

Intervention	ER −20% Av. events (M)	ER −20% Net (€bn)	ER −10% Av. events (M)	ER −10% Net (€bn)	Base case Av. events (M)	Base case Net (€bn)	ER +10% Av. events (M)	ER +10% Net (€bn)	ER +20% Av. events (M)	ER +20% Net (€bn)
O3 1g/day	0.515	25.1	0.58	28.8	0.644	32.5	0.708	36.1	0.773	39.8
O3 2g/day	0.927	44.4	1.043	51	1.159	57.6	1.275	64.2	1.391	70.8
PS 1.5g/day	1.754	87.6	1.974	100.3	2.193	113	2.412	125.7	2.632	138.4
PS 3g/day	3.007	146.2	3.383	167.9	3.759	189.7	4.135	211.5	4.511	233.3
BG 3g/day	1.604	69	1.804	80.7	2.005	92.3	2.205	103.9	2.406	115.5
Combined (base-case doses)		**181.8**		**209.8**		**237.8**		**265.8**		**293.7**

Note: ER = baseline event rate. The sensitivity applies ±10% and ±20% changes to baseline event rates while holding intervention-specific RRRs, supplementation costs, eligible populations, and other model assumptions constant. Changes in event rates therefore translate proportionally into avoidable events and gross societal cost savings, while supplementation costs remain unchanged.

7.5.3 Economic Return on Supplementation Expenditure: SC/HCCS as a Return-on-Investment Metric

The supplementation cost-to-gross-societal-savings ratio, presented earlier as a measure of geographic variation in supplementation economics, can be inverted to express the economic return on supplementation expenditure in more intuitive terms. Rather than expressing supplementation costs as a share of gross societal cost savings, the inverted metric asks: for every €1 spent on supplementation across the eligible population, how many euros of gross societal cost savings are generated? This gross benefit-cost ratio provides an intuitive representation of the economic return associated with supplementation and is readily interpretable by policymakers, health-system stakeholders, and procurement bodies.

Aggregate EU27+UK return, 2025 base year

At the 2025 base year, the three base-case interventions deliver positive gross returns per €1 of supplementation expenditure across the full EU27+UK eligible population under 100% coverage. The gross return is calculated as gross societal cost savings divided by supplementation expenditure, equivalent to the inverse of the supplementation cost-to-gross-societal-savings ratio. The net return deducts the original €1 of supplementation expenditure, representing the economic surplus generated per €1 spent. Phytosterols at 1.5 g/day deliver the highest gross return at €9.02 per €1 spent, reflecting the relationship between the modelled cardiovascular risk reduction, societal savings generated, and supplementation cost. Beta-Glucan

records the lowest gross return at €4.85 per €1 spent, reflecting its higher supplementation cost relative to the gross societal savings generated, although the resulting net economic benefit remains strongly positive.

Intervention	Supplement cost / gross societal savings	Gross societal savings per €1 spent	Net benefit per €1 spent
Omega-3 EPA+DHA 1 g/day	11.40%	€ 8.77	€ 7.77
Omega-3 EPA+DHA 2 g/day	12.60%	€ 7.94	€ 6.94
Phytosterols 1.5 g/day	11.10%	€ 9.02	€ 8.02
Phytosterols 3 g/day	12.90%	€ 7.75	€ 6.75
Beta-Glucan 3 g/day	20.60%	€ 4.85	€ 3.85

Table 7.4.3.1 - Aggregate EU27+UK return, 2025 base year

Geographic variation in return

The gross societal savings generated per €1 spent vary materially across the 28 EU27+UK geographies, driven primarily by country-level differences in societal cost per incident MACE case relative to supplementation expenditure. For Omega-3 at 1 g/day, gross societal savings range from approximately €13.0 per €1 spent in France, where higher societal CVD costs per incident case increase the savings generated relative to supplementation expenditure, to approximately €4.0 per €1 spent in Croatia, where lower societal costs per incident case reduce the economic return. The full country-level range across all five scenarios is presented below.

Country	O3 1g gross return (€/€1)	PS 1.5g gross return (€/€1)	BG 3g gross return (€/€1)
France	€ 13.00	€ 13.20	€ 7.00
Finland	€ 11.60	€ 11.80	€ 6.30
Austria	€ 11.40	€ 11.50	€ 6.10
Germany	€ 10.60	€ 10.80	€ 5.70
Sweden	€ 10.50	€ 10.70	€ 5.70

Table 7.4.3.2 - Aggregate EU27+UK return, 2025 base year

Even in the least favourable market, Croatia, every €1 spent on Beta-Glucan supplementation generates approximately €2.2 in gross societal cost savings, while every €1 spent on Omega-3 or Phytosterol supplementation generates approximately €4.0 to €4.6. The economic case therefore remains positive in every national market under current retail pricing, with no geography generating less than €2 in gross societal cost savings per €1 spent across any of the three base-case interventions.

Policy implications of the return metric

The benefit-cost framing provides an intuitive way of communicating the economic results to health authorities, procurement bodies, and other policy stakeholders. Under the full societal perspective, supplementation at the base-case doses generates approximately €4 to €13 in gross societal cost savings for every €1 of supplementation expenditure, depending on the intervention and national cost structure.

These results illustrate the scale of the potential economic value associated with avoided cardiovascular events relative to the expenditure required to provide supplementation across the eligible population.

The gross savings figures presented here are derived from the full societal cost perspective applied throughout this report. Under the narrower H&SC-only perspective, which excludes informal care and productivity losses, gross H&SC savings per €1 spent fall to approximately €4.8 for Omega-3, €4.9 for Phytosterols, and €2.7 for Beta-Glucan at EU27+UK aggregate level. After deducting the supplementation expenditure itself, the corresponding net benefits per €1 spent are approximately €3.8, €3.9, and €1.7, respectively. The H&SC-only analysis therefore provides a more conservative assessment of the economic return when only direct health and social care savings are considered.

7.6 Summary and Policy Implications

7.6.1 Summary of findings

The cost-savings model presented in this report quantifies the full societal economic value of cardiovascular disease prevention through three food supplement interventions, Omega-3 EPA+DHA, Phytosterols, and Beta-Glucan, across the EU27+UK for the period 2025 to 2035. The analysis is structured around a clinical pathway framework that translates intervention-specific RRRs derived from the published evidence base into avoidable incident MACE events, gross societal cost savings, supplementation costs, and net economic benefit at country and aggregate level.

At the 2025 base year, the three base-case interventions collectively generate an estimated 4.842 million avoidable incident MACE events per year across the EU27+UK eligible populations of 34.6 million for Omega-3 and 83.7 million for Phytosterols and Beta-Glucan. Gross societal cost savings total €279.9 billion annually, €36.6 billion for Omega-3, €127.1 billion for Phytosterols, and €116.2 billion for Beta-Glucan, representing the full societal economic value of the CVD burden that supplementation at base-case doses could prevent under full eligible-population coverage. After deducting supplementation costs at the retail prices applied in the model, net benefit is positive across all three interventions and all 28 EU27+UK geographies: €32.5 billion for Omega-3, €113.0 billion for Phytosterols, and €92.3 billion for Beta-Glucan in 2025, a combined €237.8 billion annually. Over the 2025–2035 projection window, cumulative net benefit approximates €408 billion for Omega-3, €1,416 billion for Phytosterols, and €1,159 billion for Beta-Glucan, a combined €2,984 billion across the three interventions.

The structural driver of positive net benefit across the base-case scenarios is the relationship between the societal CVD cost per incident case and supplementation expenditure. Supplementation costs represent approximately 11% to 21% of gross societal cost savings across the three interventions, corresponding to supplementation cost-to-gross-societal-savings ratios of 0.114 for Omega-3, 0.111 for Phytosterols, and 0.206 for Beta-Glucan. The sensitivity analysis confirms that net benefit remains positive under the alternative assumptions tested. Under the low-bound RRR scenario, net benefit is €17.8 billion for Omega-3, €76.7 billion for Phytosterols, and €48.7 billion for Beta-Glucan; under the H&SC-only cost perspective, it is €15.8 billion, €55.6 billion, and €39.8 billion respectively; and under 50% population coverage, it is €16.2 billion, €56.5 billion, and €46.1 billion respectively.

The geographic analysis shows positive net benefit across all 28 EU27+UK markets under the base-case assumptions. The largest absolute net benefits are concentrated in the larger eligible populations, including Germany, France, Italy, the UK, and Spain, while variation in the supplementation cost-to-gross-societal-savings ratio primarily reflects differences in supplementation expenditure relative to country-level societal CVD costs per incident case.

7.6.2 Policy implications

The findings of this analysis carry several implications for policymakers, health system stakeholders, ingredient manufacturers, and supplement market participants across the EU27+UK.

The estimated €279.9 billion in gross societal cost savings in 2025, rising to €360.8 billion by 2035, together with approximately €2,984 billion in cumulative net benefit across the three base-case interventions over 2025–2035, illustrate the scale of the economic burden potentially addressable through the modelled supplementation strategies. At full eligible-population coverage, the interventions collectively generate approximately 4.842 million avoidable incident MACE events in the 2025 base year. These results should be interpreted as the economic opportunity under the modelled assumptions rather than as a forecast of realised population uptake.

For supplement pricing and market access, the analysis shows positive net benefit across all 28 EU27+UK geographies under the base-case assumptions. At EU27+UK aggregate level, supplementation expenditure represents approximately 11% of gross societal cost savings for Omega-3 and Phytosterols and approximately 21% for Beta-Glucan. Country-level ratios vary more substantially as a result of differences in supplementation expenditure and societal CVD costs per incident case. This variation highlights the importance of national cost structures when interpreting the economic return from supplementation and assessing potential approaches to improving affordability and access.

A range of policy and market mechanisms could potentially reduce supplementation costs to eligible individuals, including VAT treatment, institutional procurement, reimbursement or co-pay arrangements for defined populations, employer-based programmes, pharmacy own-label competition, and reductions in ingredient or manufacturing costs. The economic implications of such mechanisms would depend on their design, eligibility criteria, implementation costs, and national market conditions and are not independently modelled in this analysis.

For health technology assessment and reimbursement discussions, the cost-perspective sensitivity analysis is particularly relevant. Under the narrower H&SC-only perspective, which excludes informal care and productivity losses, net benefit remains positive at EU27+UK aggregate level at €15.8 billion for Omega-3, €55.6 billion for Phytosterols, and €39.8 billion for Beta-Glucan. These estimates are materially below those generated under the full societal perspective, demonstrating the importance of the selected cost perspective when interpreting the economic impact of preventive supplementation.

The sensitivity analysis also demonstrates the importance of the assumed intervention efficacy. Under the RRR ranges tested, net benefit remains positive for all three base-case interventions, ranging from €17.8 billion to €47.1 billion for Omega-3 at 1 g/day, €76.7 billion to €149.3 billion for Phytosterols at 1.5 g/day,

and €48.7 billion to €103.2 billion for Beta-Glucan at 3 g/day. This sensitivity highlights the value of continued clinical research to refine estimates of cardiovascular risk reduction at food-supplement doses. For Beta-Glucan, supplementation expenditure represents a larger share of gross societal savings than for the other two base-case interventions; reductions in ingredient, formulation, or delivery costs would therefore improve its economic return, all else being equal.

Overall, the analysis indicates that the economic conclusions remain positive across the principal sensitivity assumptions tested, while their magnitude is influenced by intervention efficacy, supplementation cost, eligible-population definition, baseline event rates, population coverage, and the economic cost perspective adopted. The results therefore provide a framework for assessing the potential scale and robustness of the economic opportunity rather than a prediction of realised savings under current market conditions.

8 APPENDIX

8.1 The Epidemiologic Burden of CVD in the EU27+UK

8.1.1 CVD Epidemiology

This section assembles the foundational evidence base on which all subsequent analysis in this report rests. It documents the scale and geographic distribution of cardiovascular disease burden across the EU27 and UK through four interconnected analytical layers: the epidemiological burden of Cardiovascular Disease (CVD), Coronary artery disease (CAD) (used interchangeably with ischaemic heart disease (IHD) throughout this report) and stroke by country and sex; the cardiometabolic marker profiles that define the proximate biological determinants of that burden; the behavioural and environmental risk factors that drive those markers; and a composite cardiovascular risk index that synthesises all dimensions into a single, operationally usable country ranking. Taken together these layers establish that cardiovascular disease burden across the study geography is not uniformly distributed but is geographically concentrated, structurally determined, and directly traceable to modifiable upstream risk factors, findings that define both the eligible population and the geographic stratification of the cost-savings model presented in subsequent chapters.

CVD represents a pervasive and unevenly distributed health burden across the EU and UK. Analysis of 2023 country-level data covering 27 EU Member States and the UK reveals substantial variation in both the prevalence and incidence of CVD across geographies, sexes, and regional clusters, with important implications for the population denominators underpinning this study's cost-savings model.

Overall prevalence

CVD prevalence among male's ranges from 10.9% in Cyprus to 19.5% in France, with an EU27+UK unweighted mean of 14.5%. Among females, prevalence ranges from 7.9% in Cyprus to 14.5% in France, with a mean of 11.0%. Across both sexes the male-to-female prevalence ratio averages 1.32-fold, a consistent differential of approximately 3.5 percentage points, confirming that at any given time roughly one in seven adult males across the study geography is living with established cardiovascular disease, while female prevalence affects more than one in ten adult women on average.[48]

The geographic distribution of CVD prevalence does not map straightforwardly onto the patterns of cardiovascular mortality documented later in this chapter, and this divergence is analytically important.

The highest male prevalence rates are concentrated in a cluster that spans both Western and Eastern European countries simultaneously: France (19.5%), Austria (17.5%), Lithuania (17.2%), Sweden (17.2%), Germany (17.0%), Bulgaria (16.9%), Czechia (16.7%), and Hungary (16.6%) all record male prevalence above 16%.

[48] IHME/Global Health Data Exchange (GHDx)

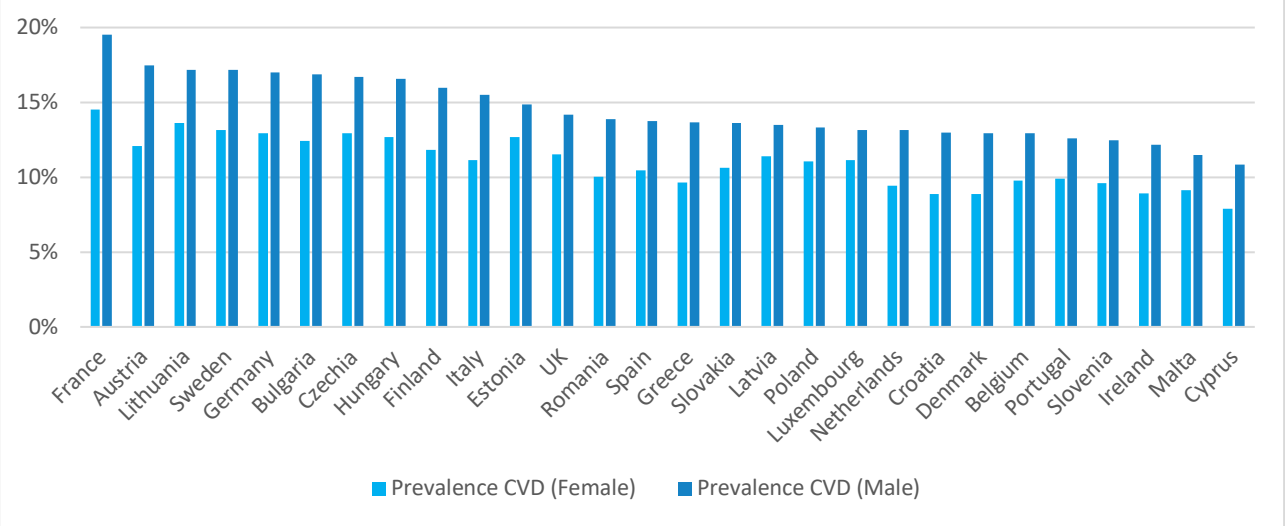

Figure 8.1.1.1: Prevalence of CVD in EU27+UK in 2023

This co-presence of Western and Eastern European countries in the same high-prevalence cluster reflects a fundamental difference between CVD prevalence and CVD mortality as epidemiological metrics. Indeed, prevalence captures the stock of living people with established cardiovascular disease at a given point in time and is therefore shaped not only by incidence but by survival:

- In Western European countries with effective acute care, cardiac rehabilitation, and long-term secondary prevention, high incidence translates into a large surviving prevalent population.
- In Eastern European countries with higher case-fatality rates and more limited post-event care, comparable or higher incidence produces a different prevalence profile, one where the burden is expressed more through premature death than through a large surviving population managing chronic CVD.

This distinction is directly relevant to the cost-savings model developed in the following chapter: the preventable burden in high-mortality Eastern European countries is concentrated in incident events and deaths, while the preventable burden in lower-mortality Western European countries includes a larger component of cardiovascular event reduction in an already-prevalent population.

The lowest male prevalence rates are observed in Cyprus (10.9%), Malta (11.5%), Ireland (12.2%), Slovenia (12.5%), and Portugal (12.6%), countries that combine relatively younger demographic profiles with comparatively lower historical CVD incidence. Among females, the same broad pattern holds, with France (14.5%), Lithuania (13.6%), Sweden (13.2%), Germany (13.0%), Czechia (12.9%), Estonia (12.7%), and Hungary (12.7%) recording the highest female prevalence, and Cyprus (7.9%), Ireland (8.9%), Denmark (8.9%), Croatia (8.9%), and Malta (9.1%) the lowest.

Incidence, new cases entering the disease pathway.

Annual CVD incidence,[10] the rate of new cases per year as a proportion of the population, ranges from 0.23% to 0.42% among males and from 0.16% to 0.29% among females across the study geography, with EU27+UK unweighted means of 0.30% and 0.21% respectively.

At population scale, and across the combined EU27+UK adult population of approximately 360 million, this translates to an estimated 537,000 new male CVD cases and 388,000 new female cases annually, the incident population against which preventive supplementation scenarios are modelled in this study. Expressed differently, roughly three in every thousand adult males and two in every thousand adult females enter the CVD disease pathway as new cases each year, generating a continuous stream of acute events, hospitalisations, and long-term disease management costs that upstream preventive intervention can reduce.

The highest incidence rates are recorded in Bulgaria (0.42% male, 0.29% female) and Romania (0.38% male, 0.27% female), both of which record the most severe compound cardiovascular risk factor burdens in the composite index developed in the following section. Austria (0.37% male, 0.24% female), Germany (0.37% male, 0.25% female), Italy (0.36% male, 0.23% female), and Lithuania (0.36% male, 0.25% female) also record elevated incidence, alongside Sweden (0.35% male, 0.24% female).

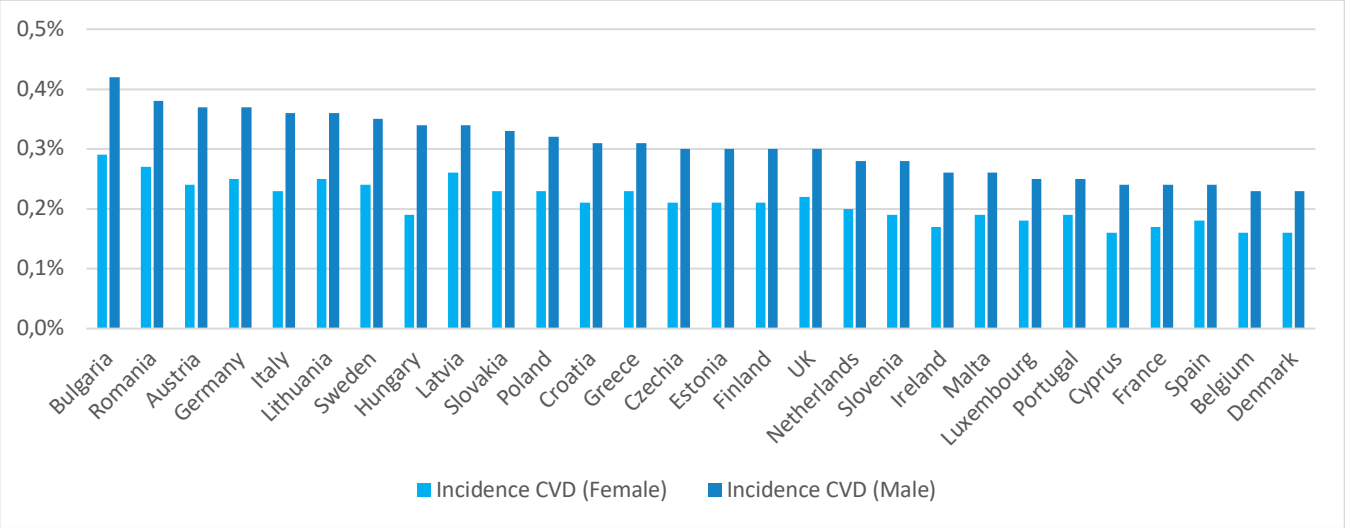

Figure 8.1.1.2: Incidence of CVD in EU27+UK in 2023

As with the prevalence, elevated incidence in Western and Northern European countries such as Austria, Germany, and Sweden does not straightforwardly reflect a higher underlying disease burden, it partly reflects older demographic structures, higher diagnostic capture rates, and longer survival after previous cardiovascular events that return individuals to incidence counts.

The distinction between incidence driven by poor risk factor control and incidence driven by a large ageing survivor population carries direct implications for the type and targeting of preventive intervention required in each geography.

Sex differentials and the gender gap

A consistent and statistically meaningful sex differential in CVD burden is observed across all 28 geographies. Male prevalence exceeds female prevalence in every country, with the absolute gap ranging from 2.00 percentage points in Luxembourg to 5.40 percentage points in Austria. The widest male-to-female prevalence gaps are recorded in Austria (5.40pp), France (5.00pp), Bulgaria (4.50pp), Italy (4.30pp), and Finland (4.20pp), while the narrowest gaps are observed in Luxembourg (2.00pp), Latvia (2.10pp), Estonia (2.20pp), Poland (2.20pp), and Malta (2.40pp). In relative terms, the male-to-female prevalence ratio reaches 1.46-fold in Croatia and 1.45-fold in Austria and Denmark, while the lowest ratios are recorded in Estonia (1.17x) and Latvia (1.18x).

The narrower gender gap in the Baltic states, Estonia and Latvia in particular, does not reflect uniformly low CVD burden. It rather reflects a pattern in which female CVD prevalence remains relatively elevated in those populations. Latvia's female prevalence of 11.4% and Estonia's female prevalence of 12.7% both exceed the EU27+UK unweighted female mean of 11.0%, meaning the compressed gender gap in these countries is driven by an upward shift in female risk rather than by a downward shift in male risk. This is an analytically important distinction: a narrow gender gap in a high-burden country signals elevated female risk, whereas a narrow gap in a lower-burden country such as Luxembourg reflects a more favourable overall environment for both sexes. This pattern is consistent with the broader mortality data presented later in this chapter, which documents excess cardiovascular mortality among women in post-Soviet countries relative to Western European peers.

For incidence, the sex differential is similarly consistent, with male incidence exceeding female incidence in every country. The absolute gap ranges from 0.06 percentage points in Portugal and Spain to 0.15 percentage points in Hungary, while in relative terms the male-to-female incidence ratio ranges from 1.31-fold in Latvia to 1.79-fold in Hungary. Hungary presents the most pronounced gender asymmetry in incidence in the entire dataset, a male rate of 0.34% against a female rate of 0.19%, a 1.79-fold relative differential, likely reflecting the country's well-documented compound cardiovascular risk factor exposure among working-age males, including high rates of tobacco use, obesity, and hypertension. Austria (1.54x), Italy (1.57x), and Ireland (1.53x) also record elevated relative incidence ratios, suggesting that the male cardiovascular incidence disadvantage is particularly acute in countries with older demographic structures and persistently high male behavioural risk factor burdens.

Regional patterns and modelling implications

Three broad regional patterns emerge from the combined prevalence and incidence data. The incidence-to-prevalence ratio, the annual rate of new cases as a proportion of the existing disease stock, provides an analytically useful lens for distinguishing between countries where high prevalence primarily reflects a large surviving CVD population and countries where high incidence reflects a fast-moving disease pipeline driven by ongoing risk factor exposure.

The first pattern characterises Western and Northern European countries including France, Austria, Sweden, Germany, Finland, and Italy. These countries combine high male prevalence, ranging from 15.5% in

Italy to 19.5% in France, with moderate to high incidence and, in the case of France particularly, a comparatively low incidence-to-prevalence ratio. France's male i/p ratio of 1.23 is the lowest in the dataset, reflecting a large established CVD pool that is replenished relatively slowly by new cases, consistent with a population in which decades of effective acute care and secondary prevention have sustained a large surviving prevalent population. Austria (i/p 2.11), Germany (2.18), Sweden (2.04), and Finland (1.88) present a more balanced picture of high prevalence combined with ongoing incidence generation, reflecting ageing populations with both a large existing disease burden and sustained new case volumes.

The second pattern characterises Central and Eastern European countries. Romania records the highest incidence-to-prevalence ratio in the dataset at 2.73, followed by Latvia (2.52), Bulgaria (2.49), Slovakia (2.43), Poland (2.41), and Croatia (2.39). In these countries a comparatively lower or moderate prevalence stock is combined with high absolute incidence rates, confirming that the disease pipeline is actively accelerating, driven by elevated and undertreated exposure to the modifiable risk factors documented in the composite risk index. Bulgaria's male incidence of 0.42% combined with a prevalence of 16.9% and an i/p ratio of 2.49, and Romania's male incidence of 0.38% against a prevalence of 13.9% and an i/p ratio of 2.73, place these countries in a qualitatively different epidemiological position from France or Finland: their CVD burden is not primarily a legacy survivor pool but an actively replenishing disease pipeline in which preventive intervention has the highest potential marginal return per person reached.

The third pattern characterises Southern European and smaller Western European countries including Cyprus, Malta, Spain, Portugal, Belgium, Denmark, and Ireland. These countries record both lower prevalence, male prevalence ranging from 10.9% in Cyprus to 13.8% in Spain, and lower absolute incidence, pointing to a more favourable cardiovascular risk environment overall. Their i/p ratios span a broad range, from 1.74 in Spain to 2.26 in Malta and 2.20 in Cyprus, suggesting heterogeneity within this group that national averages partially obscure.

These regional differentials carry direct implications for the cost-savings model.

- Countries with the highest incidence rates, Bulgaria, Romania, Austria, Germany, Italy, Lithuania, represent the populations most likely to generate near-term CVD events that targeted supplementation could prevent.
- Countries with the highest i/p ratios, Romania, Latvia, Bulgaria, Slovakia, Poland, Croatia, represent geographies where the disease pipeline is most actively advancing and where primary prevention delivers the greatest event-reduction per supplementation user.
- Countries with the highest prevalence, France, Austria, Lithuania, Sweden, Germany, represent the largest pools of individuals who may benefit from risk factor reduction to slow disease progression and reduce recurrent event rates in an established CVD population.

The EU27+UK unweighted mean prevalence of 14.49% in males and 11.02% in females, combined with mean incidence of 0.30% and 0.21% respectively, forms the central epidemiological background for this report. Country-specific incidence rates are the primary driver of the ER baseline applied in the cost-savings model, with the 55-plus age group accounting for approximately 90% of total MACE incidence across the EU27+UK, as documented in section 6.10.

8.1.2 Epidemiology of Stroke in the EU27 and UK, 2023

Stroke represents the second major acute manifestation of CVD within the scope of this study,10 alongside coronary artery disease (CAD), and constitutes a significant component of the direct healthcare costs and productivity losses quantified in the economic model.

Analysis of 2023 country-level stroke prevalence and incidence data across all 28 geographies reveals a disease that, while lower in absolute prevalence than coronary artery disease, generates disproportionately high per-case costs through acute hospitalisation, long-term care dependency, and permanent disability.

Overall prevalence

Stroke prevalence among male's ranges from 1.2% in Luxembourg to 2.9% in Bulgaria, with an EU27+UK unweighted mean of 1.8%. Among females, prevalence ranges from 0.9% in Luxembourg to 2.2% in Bulgaria, with a mean of 1.30%. These figures indicate that, on average, approximately one in 55 adult males and one in 77 adult females across the study geography is living with the sequelae of a prior stroke at any given point in time, a population characterised by high rates of disability, dependency, and recurrent cardiovascular risk.

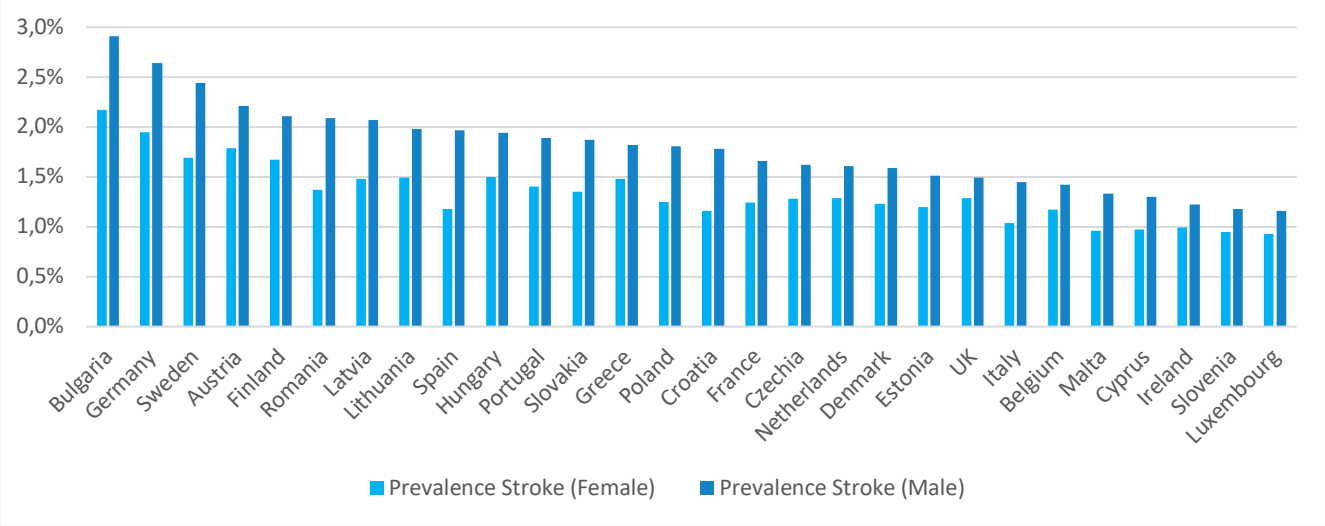

Figure 8.1.2.1: Prevalence of Stroke in EU27+UK in 2023

The highest male stroke prevalence rates are concentrated in Bulgaria (2.9%), Germany (2.6%), Sweden (2.4%), Austria (2.2%), Finland (2.1%), Romania (2.1%), and Latvia (2.1%). The presence of Germany and Sweden at the upper end of this distribution alongside Eastern European countries is notable and reflects distinct mechanisms: in Germany and Sweden, high prevalence is predominantly driven by demographic ageing and a large stock of stroke survivors benefiting from improved acute care and long-term survival, while in Bulgaria, Romania, and Latvia it reflects both higher incidence rates and historically less developed stroke rehabilitation infrastructure. Among females, the highest prevalence rates follow a similar geographic pattern, with Bulgaria (2.2%), Germany (2.0%), Austria (1.8%), Sweden (1.7%), and Finland (1.7%) recording the highest burdens.

At the lower end of the prevalence spectrum, Luxembourg (1.2% male, 0.9% female), Slovenia (1.2% male, 1.0% female), Cyprus (1.30% male, 1.0% female), Malta (1.3% male, 1.0% female), and Ireland (1.2% male, 1.0% female) record the lowest stroke prevalences. These countries combine relatively younger demographic profiles with favourable cardiovascular risk environments and, in several cases, small population sizes that limit absolute case numbers.

Incidence, new stroke events entering the disease pathway

Annual stroke incidence ranges from 0.03% to 0.13% among males and from 0.02% to 0.09% among females across the study geography, with EU27+UK unweighted means of 0.05% for males and 0.04% for females. Stroke incidence is substantially lower in absolute terms than CAD incidence, consistent with its epidemiological classification as a less frequent but higher-consequence acute event generating longer average hospital stays, higher long-term care costs, and greater permanent disability per case.

The highest male incidence rates are observed in Bulgaria (0.13%), Romania (0.10%), Latvia (0.08%), Lithuania (0.07%), and Croatia (0.06%), alongside Germany, Greece, Hungary, Poland, Slovakia, Sweden, and Spain at 0.06%. The dominance of Eastern European and Baltic countries at the top of the incidence distribution reflects the well-documented gradient in stroke risk across Europe, driven by higher rates of uncontrolled hypertension, smoking, atrial fibrillation, and elevated triglycerides in those populations, all modifiable risk factors that overlap directly with the intervention targets of Omega-3 EPA+DHA supplementation through its blood pressure and triglyceride-lowering mechanisms.

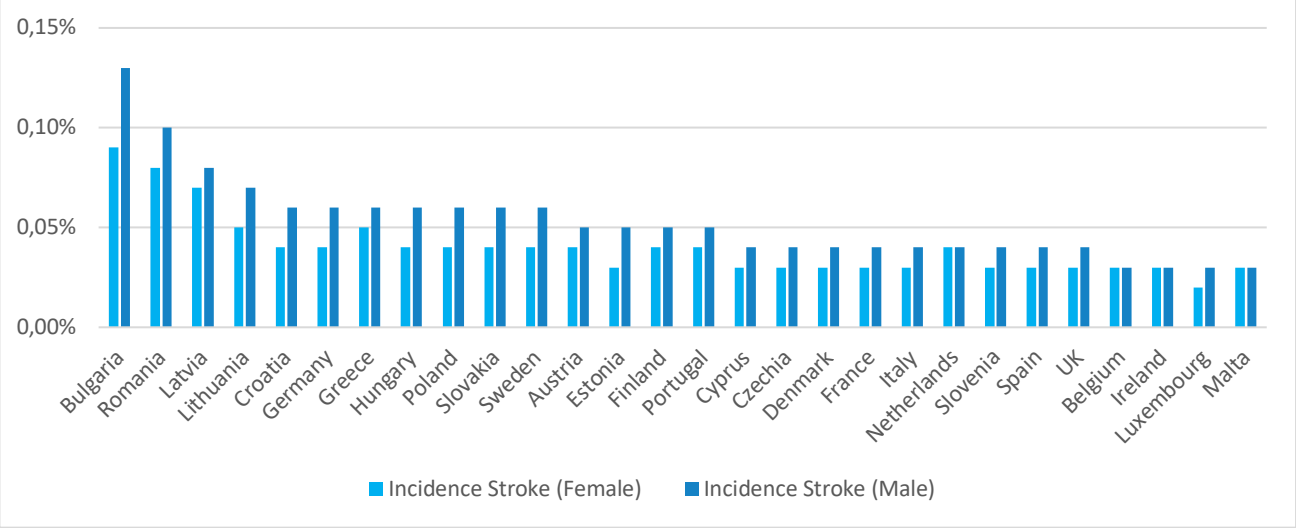

Figure 8.1.2.2: Incidence of Stroke in EU27+UK in 2023

Among females, the highest incidence rates are observed in Bulgaria (0.09%), Romania (0.08%), Latvia (0.07%), and Lithuania (0.05%), reinforcing the Eastern European and Baltic cluster as the most acute priority geography for preventive intervention. The lowest incidence rates, 0.02% to 0.03% in Luxembourg,

Ireland, Belgium, Malta, Slovenia, and several Western European countries, reflect both favourable risk environments and, in smaller countries, the statistical limitations of low absolute event numbers.

Sex differentials

The male – female differential in stroke burden is less pronounced than that observed for coronary artery disease, reflecting the well-established epidemiological pattern in which stroke affects both sexes more equally than CHD, particularly at older ages when female incidence increases substantially relative to male incidence. Male prevalence nonetheless exceeds female prevalence in every country, with absolute gaps ranging from 0.20 percentage points in the UK to 0.74 percentage points in Bulgaria and 0.69 percentage points in Germany. The widest male–female prevalence gaps are found in Bulgaria (0.74 pp), Germany (0.69 pp), Sweden (0.75 pp), and Austria (0.42 pp), while the narrowest are recorded in the UK (0.20 pp), Belgium (0.25 pp), and Ireland (0.23 pp).

The narrow gender gap in the UK and Belgium is consistent with evidence that stroke sex differentials narrow in populations with higher rates of female hypertension management and broader participation of women in preventive healthcare programmes. It may also partially reflect the statistical artefact of greater female longevity generating a larger pool of elderly female stroke survivors who elevate the female prevalence denominator relative to countries with less complete post-stroke follow-up.

For incidence, the sex differential is narrow across almost all countries, with male rates exceeding female rates by only 0.01 to 0.04 percentage points in most geographies. Spain presents an analytically unusual profile, with male incidence (0.04%) equal to female incidence (0.03%) and male stroke prevalence (2.0%) substantially higher than female prevalence (1.2%), the widest proportional prevalence gap in the dataset relative to the narrow incidence differential, suggesting a historical accumulation of male stroke survivors in a country with low current new-case rates, consistent with Spain's trajectory of declining stroke incidence over recent decades driven by improved hypertension and lipid management.

Regional patterns and modelling implications

The stroke data reinforce the three-cluster regional structure identified in the CAD analysis, albeit with some important distinctions. Eastern European and Baltic countries, Bulgaria, Romania, Latvia, Lithuania, again record both the highest prevalence and highest incidence, and represent the geographies where blood pressure lowering through Omega-3 EPA+DHA supplementation could generate the largest reductions in new stroke events. The large Western European economies, Germany, Austria, Sweden, show high prevalence driven by demographic ageing and superior long-term stroke survival, but moderate incidence, pointing to a large pool of secondary prevention candidates in whom risk factor management through supplementation could reduce recurrent event rates and associated long-term care costs. Southern and smaller Western European countries, France, Spain, Luxembourg, Slovenia, Cyprus, show the most favourable stroke profiles, though their large absolute populations still generate meaningful aggregate event volumes.

For the purposes of this study's economic model, the EU27+UK unweighted mean stroke prevalence of 1.8% among males and 1.3% among females, combined with mean incidence rates of 0.05% and 0.04% respectively, informs the stroke-specific cost component of the total CVD cost-savings calculation. Given that stroke generates the highest per-case costs of any cardiovascular event type, driven by acute inpatient care, rehabilitation, long-term disability support, and productivity losses from permanent neurological impairment, even modest reductions in stroke incidence attributable to risk factor modification through supplementation translate into substantial absolute cost savings at the EU27+UK population level, as detailed in the modelling results presented in subsequent sections.

8.1.3 Epidemiology of Ischaemic Heart Disease in the EU27 and UK, 2023

Ischaemic heart disease (IHD), used interchangeably with coronary artery disease (CAD) throughout this report, encompasses the full spectrum of myocardial ischaemic conditions, including stable angina, silent ischaemia, and acute coronary syndromes. It represents the broadest coronary disease category in this study, subsuming and extending beyond narrower acute event definitions, and constitutes the single largest driver of cardiovascular hospitalisation, premature mortality, and productivity loss across the EU27 and UK.

Overall prevalence

IHD prevalence among male's ranges from 3.3% in Cyprus to 11.5% in Lithuania, with an EU27+UK unweighted mean of 6.6%. Among females, prevalence ranges from 1.5% in Cyprus to 9.7% in Lithuania, with a mean of 4.2%. These figures indicate that approximately one in fifteen adult males and one in twenty-four adult females across the study geography is living with ischaemic heart disease at any given point, a population substantially larger than that captured by acute event registries alone, as it encompasses the full stock of subclinical and stable ischaemic presentations not recorded in narrower coronary artery disease datasets.

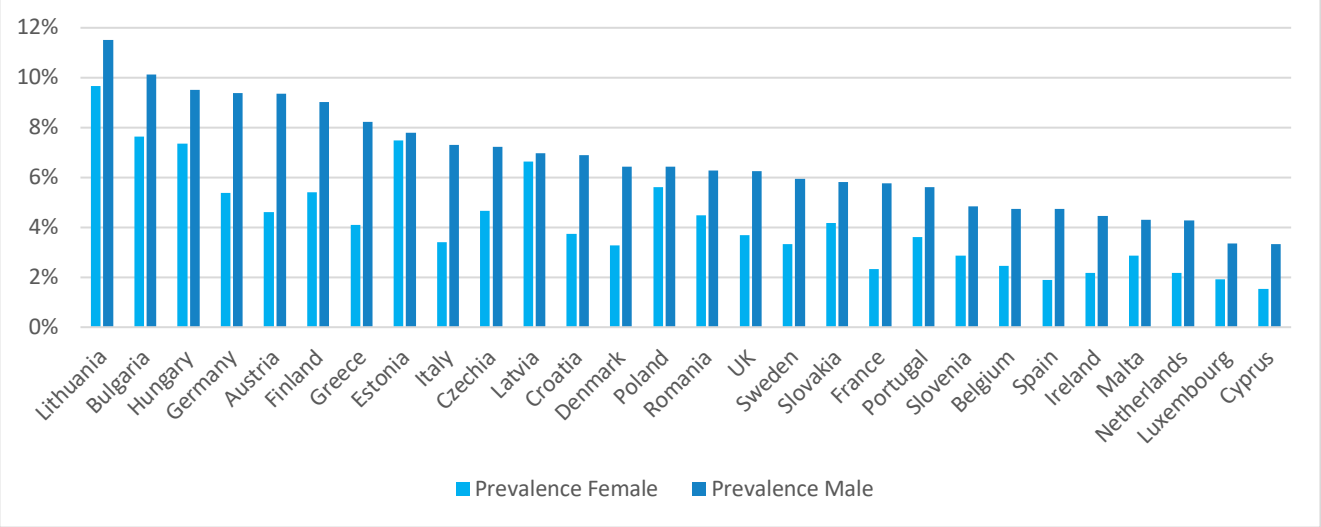

Figure 8.1.3.1: Prevalence of IHD in EU27+UK in 2023

The highest male IHD prevalence rates are concentrated in Lithuania (11.5%), Bulgaria (10.1%), Hungary (9.5%), Germany (9.4%), Austria (9.4%), Finland (9.0%), Greece (8.2%), and Estonia (7.8%). Two structurally distinct epidemiological dynamics operate within this group. In the Eastern and Baltic cluster, Lithuania, Bulgaria, Hungary, and Estonia, high prevalence reflects an upstream risk environment characterised by elevated triglycerides, hypertension, high tobacco use, and historically under-resourced primary prevention infrastructure, generating a large surviving disease population with inadequate secondary prevention coverage. In Germany, Austria, and Finland, high prevalence is driven by a different mechanism: large ageing patient populations sustained by effective acute care and cardiac rehabilitation systems, accumulating a high disease stock even where age-standardised incidence has moderated. Lithuania's male prevalence of 11.5%, the highest in the dataset and 73% above the EU27+UK mean, reflects the compounding of all major modifiable cardiovascular risk factors within a single national context.

Among females, Lithuania again leads at 9.66%, followed by Bulgaria (7.6%), Estonia (7.5%), Hungary (7.4%), Latvia (6.6%), Poland (5.6%), and Finland (5.4%). The female mean of 4.2% is notably higher than typically assumed in Western European clinical framing, driven by the elevated female IHD burden in Eastern and Baltic Member States. The Eastern and Baltic cluster records a female mean prevalence of 6.1%, more than double the Western and Nordic mean of 3.0% and the Southern European mean of 2.8%, confirming that the geographic concentration of IHD burden is not a male-specific phenomenon.

At the lower end of the prevalence spectrum, Cyprus (3.3% male, 1.5% female), Luxembourg (3.4% male, 1.9% female), Netherlands (4.3% male, 2.2% female), Malta (4.3% male, 2.9% female), and Ireland (4.4% male, 2.2% female) record the most favourable profiles. The extremely low female IHD prevalence in Cyprus (1.5%) and Spain (1.9%) reflects the combination of Mediterranean dietary patterns, lower saturated fat and sodium intake, and relatively effective hypertension management, alongside generally lower absolute cardiovascular event risk prior to age 65 in these populations.

Incidence, new IHD events entering the disease pathway

Annual IHD incidence ranges from 0.04% in Luxembourg and Spain to 0.16% in Lithuania among males, and from 0.01% in Cyprus to 0.12% in Lithuania among females, with EU27+UK unweighted means of 0.092% for males and 0.051% for females. Incidence represents the most directly intervention-relevant metric in this report: each new IHD case entering the disease pipeline represents a preventable acute coronary event or a transition from subclinical to clinical ischaemic disease that generates acute hospitalisation costs, long-term management expenditure, and productivity losses.

The highest male incidence rates are observed in Lithuania (0.16%), Bulgaria (0.15%), Italy (0.15%), Germany (0.13%), Latvia (0.13%), Poland (0.13%), Hungary (0.12%), and Romania (0.12%). Two dynamics are again at work. In the Eastern and Baltic group, Lithuania, Bulgaria, Latvia, Poland, Hungary, and Romania, high incidence reflects active accumulation of new coronary events in populations with elevated upstream risk factor burdens and weak primary prevention reach. The Eastern and Baltic cluster records a male incidence mean of 0.122%, nearly double the Western and Nordic mean of 0.063%. Germany's position in the high-incidence group (0.13%) reflects the scale of its at-risk population rather than a failure of prevention infrastructure, a large and ageing denominator generating a proportionally substantial new-

case flow even against a relatively effective clinical management environment. Italy's male incidence of 0.15%, joint second highest in the dataset alongside Bulgaria, sits against a male prevalence of 7.31% that is moderate by EU standards, pointing to an accelerating transition dynamic in which a historically protected Mediterranean population is generating new ischaemic disease at rates inconsistent with its dietary heritage, driven by the generational erosion of traditional dietary patterns and rising rates of sedentary behaviour, obesity, and metabolic syndrome in working-age males.

Among females, the highest incidence rates are found in Lithuania (0.12%), Bulgaria (0.09%), Hungary (0.09%), Latvia (0.09%), Slovakia (0.08%), and Croatia (0.07%), with the Eastern and Baltic cluster again dominating. The Eastern and Baltic female incidence mean of 0.080% is more than double the Western and Nordic mean of 0.031%, confirming the structural nature of the geographic gradient.

The lowest male incidence rates, Luxembourg (0.04%), Spain (0.04%), Cyprus (0.05%), Denmark (0.05%), and France (0.05%) are all below half the EU27+UK male mean. Among females, the same group of countries appears at the lower tail: Cyprus (0.01%), Denmark (0.02%), France (0.02%), Luxembourg (0.02%), and Spain (0.02%), confirming the consistency of the geographic risk gradient across sexes.

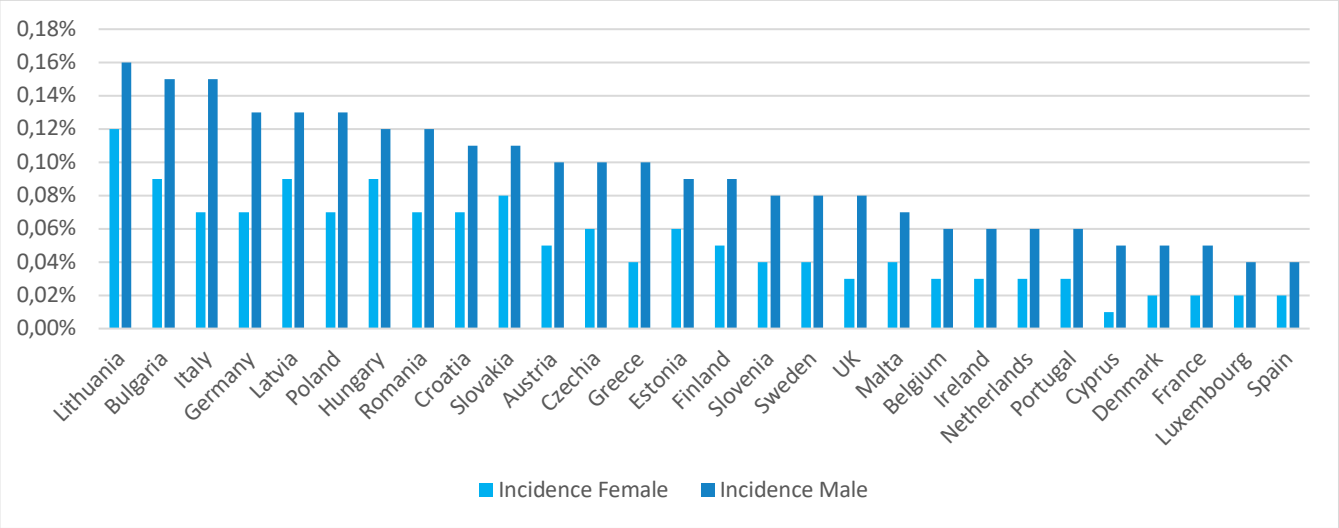

Figure 8.1.3.1: Incidence of IHD in EU27+UK in 2023

Sex differentials

The male–female differential in IHD burden is the most pronounced of the cardiovascular conditions analysed in this study. Male prevalence exceeds female prevalence in every country. The largest prevalence gaps are recorded in Austria (4.76 percentage points), Greece (4.13 pp), Germany (4.00 pp), Italy (3.90 pp), and Finland (3.63 pp), where very high male burden driven by modi fiable risk factors concentrated among working-age males coincides with female rates that, while elevated in absolute terms, remain substantially lower.

The narrowest gaps are found in Estonia (0.31 pp), Latvia (0.35 pp), and Poland (0.81 pp). These compressed differentials do not reflect low male burden but elevated female IHD prevalence: Estonian

women record 7.48% prevalence and Latvian women 6.63%, both substantially above the EU27+UK female mean of 4.23% and among the highest female rates in the dataset. This pattern signals a particularly high-risk post-menopausal female population in Baltic populations that is systematically underserved by prevention frameworks calibrated primarily around male risk profiles.

For incidence, the male-to-female ratio ranges from 1.33 in Lithuania and Hungary, where high female incidence compresses the differential, to 5.0 in Cyprus and approximately 2.5 in Denmark, France, and Greece. The low ratios in Lithuania (1.33), Hungary (1.33), Slovakia (1.38), and Latvia (1.44) reflect genuinely elevated female incidence in those countries rather than low male rates, pointing to a female cardiovascular risk burden in Eastern and Baltic populations that is proportionally high by European standards. The high ratios in Cyprus, Denmark, France, and the UK (2.67) reflect genuinely low female incidence in those countries, consistent with more favourable female cardiometabolic risk environments in Southern and Western Europe.

Regional patterns and modelling implications

The IHD data consolidate the three-cluster regional typology established across the total CVD and stroke analyses. The Eastern and Baltic cluster, Lithuania, Latvia, Estonia, Bulgaria, Hungary, Poland, Romania, Czechia, Croatia, and Slovakia, combines high prevalence with high incidence across both sexes and represents the geography of greatest absolute preventive need and the largest per-user cost-saving potential in the model. The Central and Western European economies, Germany, Austria, and the UK, record high prevalence and moderate-to-high incidence, with aggregate event volumes that are substantial by virtue of population size. Southern and smaller Western European countries, Spain, France, Luxembourg, Cyprus, the Netherlands, and Ireland, show the most favourable IHD profiles, though their populations still generate meaningful absolute disease burdens given the size of the at-risk 40–79 age cohort.

For the cost-savings model, the EU27+UK unweighted mean IHD prevalence of 6.64% among males and 4.23% among females, combined with mean incidence rates of 0.092% and 0.051% respectively, anchors the IHD-specific component of the economic analysis across all 28 geographies.

8.1.4 Metabolic & Behavioural Risk Landscape

This section characterises the upstream risk factor environment that generates the cardiovascular disease burden documented in Sections 2.1.1 to 2.1.3. The epidemiological analysis established that CVD prevalence, IHD incidence, and stroke burden are not randomly distributed across the EU27+UK but are geographically concentrated, structurally determined, and markedly worse in Eastern and Baltic Member States than in Western and Southern Europe. This section identifies why, examining seven independently validated modifiable risk indicators whose geographic distributions map directly onto the disease burden patterns already described: atherogenic lipid burden, hypertensive load, tobacco use, dietary sodium intake, physical inactivity, obesity in the over-55 population, and alcohol consumption.

Of these seven indicators, elevated triglycerides and systolic blood pressure are the primary biological targets of the omega-3 EPA+DHA supplementation intervention modelled in Section 5. Their geographic

distribution across the EU27+UK therefore determines both the size of the eligible population and the magnitude of the cost-saving potential in each Member State, making the risk factor analysis that follows a direct input into the economic model rather than background context.

The evidence establishes that the populations carrying the most adverse cardiometabolic and behavioural profiles are without exception those recording the shortest male life expectancy and the widest sex differentials in longevity across the study geography. This convergence between upstream risk exposure and downstream mortality outcomes validates the composite cardiovascular risk index that closes the section and provides the geographic stratification framework applied throughout the remainder of the report.

Cardiometabolic Risk Marker Profile of the EU27 and UK

The cardiometabolic markers analysed in this section occupy a uniquely central position in the cardiovascular risk factor framework. Unlike the behavioural and environmental risk factors examined in the next section which operate upstream through multiple intermediate pathways, the cardiometabolic markers sit at the proximate biological interface between risk factor exposure and cardiovascular event occurrence. They are simultaneously the outcome of upstream behavioural risks and the direct causal input into coronary artery disease, ischaemic heart disease, and stroke incidence. The population-level values of these markers define the scale and geographic distribution of the modifiable biological burden that preventive strategies, whether pharmacological, nutritional, or lifestyle-based, must address to reduce the cardiovascular event rates documented in the preceding epidemiological sections.

The atherogenic lipid burden

Mean total cholesterol levels across the EU27 and UK have declined substantially over the three decades from 1988 to 2018, reflecting the combined influence of statin adoption, dietary change, and public health investment in primary cardiovascular prevention.

Among males, the EU27+UK unweighted mean fell from 5.61 mmol/L in 1988 to 4.87 mmol/L in 2018; among females, from approximately 5.45 mmol/L to 4.95 mmol/L over the same period. This long-term downward trend represents genuine public health progress. However, the pace of decline has been markedly heterogeneous.

Western European countries, the UK (5.77 to 4.71 mmol/L in males), Belgium (5.80 to 4.53 mmol/L), Ireland (5.40 to 4.52 mmol/L), and Denmark (5.69 to 4.66 mmol/L), achieved reductions of approximately 1.0–1.3 mmol/L over three decades. Central and Eastern European countries made substantially less progress. In Lithuania, male total cholesterol declined from 5.82 mmol/L in 1988 to only 5.15 mmol/L in 2018, a reduction of just 0.67 mmol/L, while Latvia (5.64 to 5.13 mmol/L) and Croatia (5.49 to 5.14 mmol/L) show similarly modest trajectories.

This divergence is significant: the populations carrying the highest current lipid burden are precisely those that have benefited least from the secular trend, indicating that structural risk factor exposure rather than temporal improvement is driving their residual burden.

The primary analytical focus for characterising the atherogenic burden, however, is non-HDL cholesterol, the metric that captures all atherogenic lipoprotein particles including LDL, VLDL, and IDL, and that most closely aligns with the 2019 ESC/EAS primary treatment targets. [49]

Indeed, the ESC/EAS guideline thresholds are non-HDL below 2.6 mmol/L for very high-risk patients, below 3.4 mmol/L for high-risk patients, and below 4.0 mmol/L for moderate-risk patients. In 2018, the EU27+UK unweighted mean non-HDL cholesterol stands at 3.58 mmol/L among males and 3.38 mmol/L among females. Both values exceed or approach the high-risk guideline threshold of 3.4 mmol/L, implying that the mean adult across the study geography has an atherogenic lipid burden that would warrant active management under current guideline standards for any individual at high or exceedingly high cardiovascular risk.

Country-level heterogeneity is substantial. Among males, non-HDL cholesterol ranges from 3.13 mmol/L in Belgium, the only below the high-risk threshold, to 3.86 mmol/L in both Lithuania and Latvia. Eight countries record male non-HDL above 3.7 mmol/L: Lithuania (3.86 mmol/L), Latvia (3.86 mmol/L), Croatia (3.83 mmol/L), Bulgaria (3.78 mmol/L), Malta (3.76 mmol/L), Austria (3.76 mmol/L), France (3.75 mmol/L), and Slovenia (3.74 mmol/L). In each of these countries the mean adult male has an atherogenic lipid burden that, combined with any additional cardiovascular risk factor, smoking, diabetes, hypertension, or family history, would trigger high or very high-risk classification and intensive management under current guidelines. Among females, Portugal (3.63 mmol/L), Lithuania (3.61 mmol/L), Croatia (3.60 mmol/L), France (3.57 mmol/L), and Latvia (3.56 mmol/L) record the highest non-HDL values, concentrated in the Baltic, Central European, and, notably, Western European cluster that includes two of the most populous countries in the dataset.

The cardioprotective HDL fraction adds a further dimension to the atherogenic burden. The EU27+UK mean male HDL stands at 1.29 mmol/L in 2018, with seven countries recording values below 1.25 mmol/L, the level below which HDL is recognised as a cardiovascular risk modifier in the ESC/EAS risk stratification framework: Portugal (1.22 mmol/L), the Netherlands (1.22 mmol/L), Spain (1.23 mmol/L), Denmark (1.23 mmol/L), Italy (1.23 mmol/L), Cyprus (1.23 mmol/L), and Slovakia (1.24 mmol/L). In these countries, the combination of below-average protective capacity with above-average atherogenic burden creates a compound lipid risk profile that is most efficiently characterised through the non-HDL to HDL ratio, a validated atherogenic index capturing both dimensions simultaneously. The EU27+UK mean male non-HDL/HDL ratio stands at 2.78, with the highest values recorded in Lithuania (2.98), Malta (2.98), Italy (2.97), Slovenia (2.95), Cyprus (2.94), Slovakia (2.94), and Poland (2.91). Several Southern European countries including Italy, Cyprus, and Portugal appear in this high-risk tier not because of exceptionally elevated non-HDL but because low HDL amplifies the atherogenic burden beyond what the non-HDL value alone would

[49] Mach F. et al., 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), European Heart Journal, Volume 41, Issue 1, 1 January 2020, Pages 111–188

suggest, an analytically important distinction when characterising the full scale of the lipid-driven cardiovascular risk landscape.

The aggregate picture from the lipid data is one of a study geography in which the atherogenic burden remains clinically significant across virtually all countries, despite three decades of progress, and in which a substantial share of the adult population, concentrated in Central and Eastern European and Baltic states, but extending into major Western European economies including France and Austria, has mean non-HDL cholesterol levels that exceed the intervention thresholds defined in current clinical guidelines. This residual lipid burden, persisting despite widespread statin availability and the secular decline in mean cholesterol levels, represents the primary modifiable biological substrate of the coronary artery disease and ischaemic heart disease incidence rates documented in the preceding epidemiological analysis.

The hypertensive burden

Mean systolic blood pressure data for 2015, combined with country-level raised blood pressure prevalence data for 2019 and the SHARE 2021–2022 cohort evidence covering 68,047 adults aged 50 and over across 27 European countries, reveal a hypertensive burden that is both substantial in aggregate scale and sharply concentrated.

Hypertension is the single largest attributable risk factor for stroke globally and a major independent contributor to coronary artery disease and heart failure, making its geographic distribution directly determinant of the cardiovascular event burden documented in the previous epidemiological sections.

Mean systolic blood pressure across the EU27+UK stands at 130.5 mmHg among males and 122.6 mmHg among females. The male mean sits exactly at the 130-mmHg threshold at which the 2018 ESC/ESH guidelines define the lower boundary of Stage 1 hypertension, meaning that the average adult male across the study geography is already in the hypertensive range. Eleven countries record mean male systolic blood pressure at or above 130 mmHg: Slovenia (137.5 mmHg), Lithuania (137.3 mmHg), Croatia (137.2 mmHg), Latvia (135.7 mmHg), Estonia (135.5 mmHg), Romania (135.5 mmHg), Hungary (134.9 mmHg), Bulgaria (134.2 mmHg), Poland (134.1 mmHg), Slovakia (132.4 mmHg), and Czechia (131.6 mmHg). In the three highest-burden countries, Slovenia, Lithuania, and Croatia, mean male systolic blood pressure exceeds 137 mmHg, a level at which most adult males in those populations would be classified as hypertensive under current clinical guidelines. Among females, eight countries record mean systolic blood pressure at or above 125 mmHg: Bulgaria (129.8 mmHg), Estonia (129.5 mmHg), Croatia (127.5 mmHg), Lithuania (127.1 mmHg), Slovenia (127.0 mmHg), Romania (126.1 mmHg), Hungary (125.1 mmHg), and Latvia (125.0 mmHg).

The 2019 raised blood pressure prevalence data from Eurostat translate these continuous blood pressure distributions into population headcounts. Across the EU27+UK, mean raised blood pressure prevalence stands at 22.9% of the total adult population, approximately one in four adults, ranging from 11.6% in Ireland to 37.3% in Croatia. Twelve countries record total raised blood pressure prevalence above 25%, with the five highest all classified as Very High-risk tier: Croatia (37.3%), Latvia (31.7%), Hungary (31.5%), Lithuania (29.9%), and Bulgaria (29.7%). Across the Very High-risk tier, mean total raised blood pressure prevalence stands at 28.9%, compared with 19.9% in the Lower risk tier, a differential of nine percentage

points that directly amplifies the absolute stroke and coronary event rates documented in those populations. At the lower end of the distribution, Ireland (11.6%), Luxembourg (15.5%), the Netherlands (16.1%), France (16.5%), and Belgium (17.4%) record the most favourable profiles, consistent with their Lower or Moderate tier composite risk classifications.

The sex differential in raised blood pressure reveals a pattern of clinical relevance for the post-menopausal female population. Across the EU27+UK, mean female raised blood pressure prevalence (23.9%) modestly exceeds male prevalence (21.8%), reflecting the post-menopausal shift in blood pressure regulation driven by oestrogen withdrawal, increased arterial stiffness, and central wave reflection. This female excess is most pronounced in Latvia, where the female-male gap reaches 11.3 percentage points (36.7% versus 25.4%), the widest in the entire dataset, followed by Lithuania (7.7 pp), Bulgaria (6.3 pp), Romania (6.0 pp), and Estonia (5.9 pp). In all five countries, female raised blood pressure prevalence substantially exceeds male prevalence, creating a particularly large eligible population for blood pressure-reducing interventions among post-menopausal women in the countries that simultaneously record the highest absolute cardiovascular event burdens.

The SHARE 2021–2022 cohort data, covering 68,047 adults aged 50 and over across 27 European countries, complement the population-level prevalence data by documenting how the hypertensive burden escalates across the adult life course and varies by European region.14 Among European adults aged 50–64, 39.4% of men and 33.5% of women report a current or previous hypertension diagnosis. By ages 65–79 this rises to 62.6% of men and 63.1% of women, with the sex differential converging as the post-menopausal blood pressure increase narrows the gap seen in younger cohorts. Among adults aged 80 and over, 71.8% of men and 78.0% of women carry a hypertension diagnosis, with the female excess at this age reflecting the established shift in sex-based blood pressure trajectories driven by arterial stiffening in the oldest age groups.

The regional stratification within the SHARE data reinforces the geographic concentration documented in the country-level data. Among women aged 50–64, Central and Eastern Europe records a hypertension diagnosis prevalence of 44.1%, 12.9 percentage points above Western Europe (31.2%) and 13.7 percentage points above Southern Europe (30.4%). This CEE excess is sustained and amplifies across the life course: at ages 65–79, CEE women record 73.4% prevalence against 54.3% in Western Europe, a 19.1 percentage point gap, while at ages 80 and over, CEE (85.2%) and Southern Europe (85.5%) together record the highest regional burdens, both substantially above Western Europe (70.2%). Among men, Southern Europe produces the highest hypertension diagnosis prevalence at ages 65–79 (74.2%) and 80 and over (80.5%), driven by the convergence of high tobacco burdens, sedentary behaviour, and obesity in older Southern European male cohorts documented throughout this chapter. As the authors conclude, these regional disparities reflect broader systemic differences in healthcare infrastructure, public health policy, and upstream risk factor environments, highlighting the need for region-specific prevention strategies.14

The convergence of mean systolic blood pressure, raised blood pressure prevalence, and SHARE regional diagnosis data across three independent sources and data vintages confirms a consistent and geographically structured hypertensive burden. The countries and regions recording the highest upstream risk factor exposures, dietary sodium, physical inactivity, over-55 obesity, and alcohol, are the same countries and regions recording the highest blood pressure burden across all three data sources and across all age groups studied.

Compound cardiometabolic risk

The most significant finding to emerge from the integrated cardiometabolic marker analysis is not the level of any single marker in any single country, but the systematic co-occurrence of adverse values across multiple markers in the same geographic cluster. Lithuania, Latvia, Croatia, Bulgaria, Hungary, Romania, Slovenia, Estonia, Poland, and Slovakia consistently appear at the high-burden end of every cardiometabolic marker distribution examined in the preceding two blocks, elevated non-HDL cholesterol, low HDL cholesterol, high atherogenic index, elevated mean systolic blood pressure, and high raised blood pressure prevalence. This pattern of compound cardiometabolic risk, where every proximate biological determinant of cardiovascular event risk is simultaneously elevated above the EU27+UK mean, is not additive in its effect on absolute event probability but multiplicative, as the SCORE2 risk algorithm's interaction terms between lipid and blood pressure risk factors make explicit.

The co-occurrence of high atherogenic lipid burden and high hypertensive burden in the same populations generates a cardiovascular risk environment that substantially exceeds the sum of its individual components. An adult male in Lithuania carrying a mean non-HDL of 3.86 mmol/L and a mean systolic blood pressure of 137.3 mmHg faces a compounded absolute coronary and cerebrovascular event risk that is not merely the arithmetic sum of his lipid risk and his blood pressure risk, but a multiplicatively amplified risk reflecting the synergistic acceleration of atherosclerotic plaque progression and plaque rupture probability that the combination of dyslipidaemia and hypertension drives. This is precisely the biological mechanism underlying the disproportionately high CAD incidence (1.95% annually in males), IHD prevalence (11.54% in males), and stroke incidence (0.07% annually in males) recorded in Lithuania in the epidemiological analysis, the highest or near-highest rates in the dataset for all three conditions.

Three Western European countries, France, Austria, and Malta, represent an analytically distinct subgroup that merits specific attention within the compound risk picture. These countries do not belong to the Central and Eastern European cluster geographically, yet they appear consistently in the upper quartile of both lipid and blood pressure burden. France records male non-HDL of 3.75 mmol/L, the seventh highest in the dataset, combined with a mean male systolic blood pressure of 127.0 mmHg and a raised blood pressure prevalence of 22.0%. Austria records male non-HDL of 3.76 mmol/L and male systolic blood pressure of 127.6 mmHg. Malta records the second highest male atherogenic index in the dataset at 2.98, driven by a combination of elevated non-HDL at 3.76 mmol/L and low HDL at 1.26 mmol/L. The cardiovascular disease burden data confirm that these compound cardiometabolic profiles translate into real event burden: France records the highest total CVD prevalence in the dataset (19.51% in males), Austria the second highest (17.49% in males), and both countries feature in the upper quartile of CAD and IHD prevalence. The compound marker analysis therefore explains what the epidemiological data describe: the high cardiovascular burden in these Western European populations is not anomalous given their cardiometabolic risk marker profiles, but a predictable consequence of the sustained exposure to elevated atherogenic lipid and hypertensive burdens that the data document.

At the other end of the compound risk spectrum, Belgium, the UK, Ireland, and Denmark consistently record the most favourable profiles across all five markers, the lowest non-HDL values, the highest or near-highest HDL values, the lowest atherogenic indices, the lowest mean systolic blood pressures, and the lowest raised blood pressure prevalences in the dataset. These countries' more favourable cardiometabolic

marker profiles are consistent with their lower CVD, CAD, IHD, and stroke prevalence and incidence rates in the epidemiological analysis, confirming the internal coherence of the risk factor and disease burden data and strengthening the validity of the overall analytical framework.

Taken together, the atherogenic lipid burden, the hypertensive burden and the compound cardiometabolic risk analysis presented in this section establish that the cardiovascular disease burden documented in the preceding epidemiological sections is not distributed randomly across the EU27+UK geography but is concentrated in populations that carry systematically elevated cardiometabolic markers simultaneously.

The geographic concentration of compound cardiometabolic risk in Central and Eastern European and Baltic states, alongside pockets of elevated burden in major Western European economies, defines both the scale of the unmet preventive need and the geographic distribution of the populations for whom evidence-based risk factor management represents the most urgent public health priority.

Behavioural and Environmental Risk Factor Profile of the EU27 and UK

The cardiometabolic markers analysed in the previous section represent the proximate biological determinants of cardiovascular event risk. The behavioural and environmental risk factors examined in this section operate upstream, shaping those cardiometabolic profiles through sustained and often lifelong exposure. Tobacco use, alcohol consumption, physical inactivity, dietary patterns, and ambient air pollution do not independently cause coronary artery disease, stroke, or ischaemic heart disease in isolation, they do so primarily by elevating LDL-C, triglycerides, blood pressure, and inflammatory burden, the same markers documented as elevated and geographically concentrated before. Understanding the behavioural and environmental risk landscape therefore deepens the explanatory framework established by the cardiometabolic marker analysis and highlights the structural drivers of the compound cardiovascular risk burden in those populations.

Obesity: Prevalence, Age Gradient, and Cardiovascular Risk Amplification

Obesity, defined as a body mass index at or above 30 kg/m², constitutes one of the most consequential and rapidly worsening cardiovascular risk factors across the EU27 and UK. Its relevance to this study is threefold: Independent driver of elevated triglycerides and reduced HDL cholesterol through hepatic de novo lipogenesis and altered lipoprotein metabolism; Direct contributor to hypertension through haemodynamic and neurohormonal pathways; Promoter of insulin resistance and metabolic syndrome, both of which amplify the atherogenic lipid burden documented in the cardiometabolic marker analysis.

The age-stratified NCD-RisC 2022 data presented here, covering adults under 55 and adults over 55 across the full EU27+UK geography, reveal an obesity landscape that is both severe in its current scale and deeply concerning in its trajectory since 2002. The NCD-RisC 2022 data presented here cover two age strata, adults under and over 55, across the full EU27+UK geography, with the over-55 group carrying the greatest analytical weight given its direct correspondence to the population at highest absolute cardiovascular event risk.

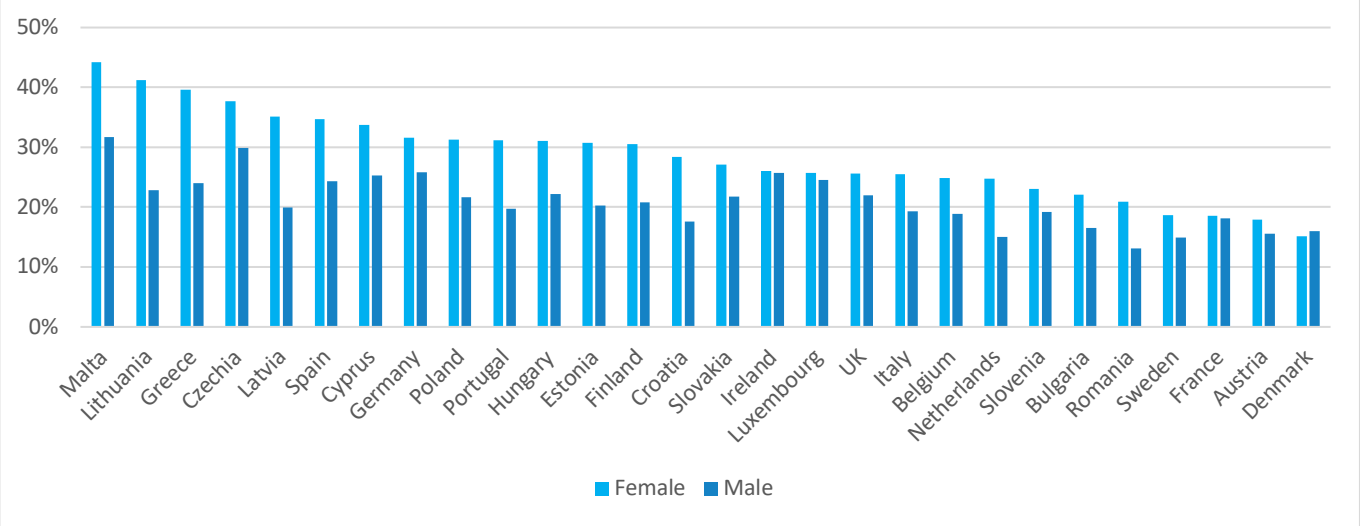

Figure 8.1.4.1: Obesity prevalence in population over 55 years old by gender in 2002

Among adults under 55, EU27+UK mean obesity prevalence stands at 21.4% in males and 16.6% in females in 2022. The highest combined prevalences are recorded in Romania (29.4%), Malta (28.6%), Hungary (26.4%), Croatia (25.7%), and Ireland (24.8%). France records the lowest combined prevalence in the dataset at 8.3%, consistent with its comparatively favourable metabolic phenotype despite elevated tobacco and lipid burdens. The male excess in obesity is largest in Slovenia (11.7 percentage points above females), Poland (9.9 pp), Croatia (9.8 pp), and Hungary (9.5 pp), reflecting higher rates of visceral adiposity accumulation in younger males in those populations.

The cardiovascular significance of the obesity burden is substantially amplified in the over-55 population. Mean combined obesity prevalence in this age group reaches 32.1% across the EU27+UK, approximately 50% higher than in the under-55 group. Female over-55 obesity exceeds 40% in eight countries.

This concentration in the post-menopausal age group is clinically significant: the convergence of oestrogen loss, post-menopausal LDL-C elevation, and high obesity prevalence creates a compounded cardiometabolic risk environment that the female CVD incidence data in the epidemiological sections likely underestimate given the historically male-skewed composition of cardiovascular trial populations.

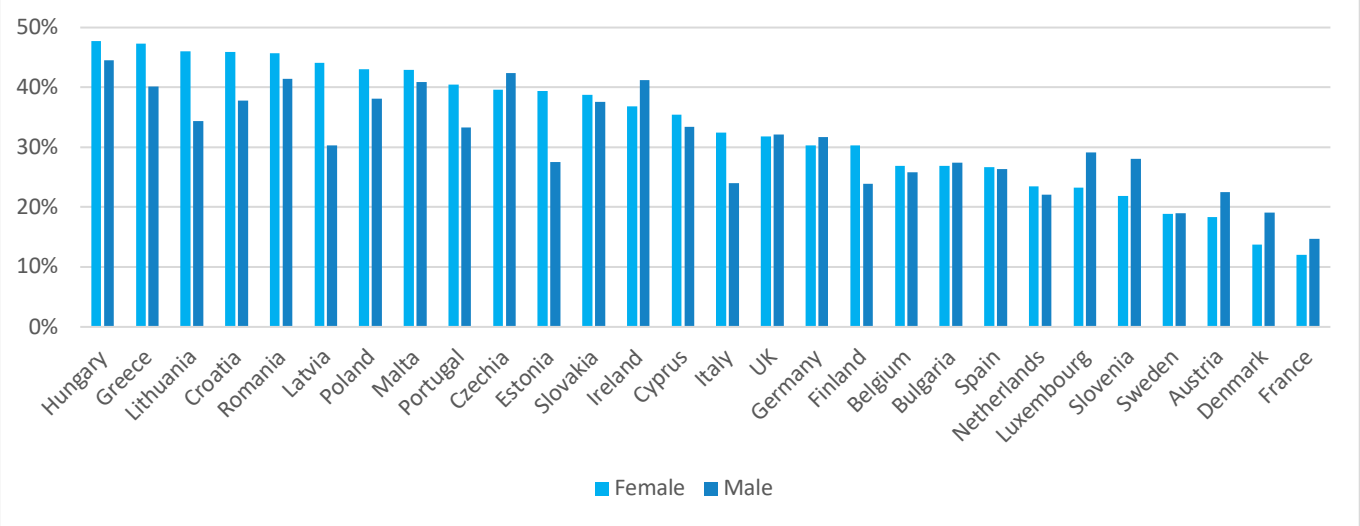

Figure 8.1.4.2: Obesity prevalence in population over 55 years old by gender in 2022

The 20-year trend from 2002 to 2022 reveals a marked deterioration in obesity prevalence across much of the EU27+UK, particularly among males. Across the 28 countries, mean male prevalence increased from 21.0% to 31.0%, compared with an increase from 28.5% to 33.2% among females. Consequently, the female–male prevalence gap narrowed substantially, from approximately 7.5 percentage points in 2002 to 2.2 percentage points in 2022. Romania recorded the largest increase among males, rising by 28.4 percentage points from 13.1% in 2002 to 41.5% in 2022, more than tripling over the period. This was followed by Hungary (+22.3 pp), Croatia (+20.2 pp), Poland (+16.5 pp), Greece (+16.2 pp), Slovakia (+15.8 pp), and Ireland (+15.5 pp). Among females, Romania again recorded the largest increase (+24.8 pp), followed by Croatia (+17.6 pp) and Hungary (+16.7 pp). The resulting 2022 burden is substantial: the simple mean of male and female prevalence reaches 32.1% across the EU27+UK, compared with 24.7% in 2002. If these trends persist, they could contribute to an increasingly adverse cardiometabolic risk environment over the 2025–2035 modelling horizon, reinforcing the importance of obesity as a contextual driver of future cardiovascular disease burden.

Tobacco Use: A Persistent and Unevenly Distributed Cardiovascular Risk Amplifier

Daily smoking remains a major independent risk factor for CVD, acting through multiple mechanisms including endothelial dysfunction, oxidative modification of LDL, platelet activation, reduced HDL cholesterol, and accelerated atherosclerosis. Its relevance extends beyond direct causation: smoking diminishes the effectiveness of lipid-lowering interventions and interacts synergistically with elevated LDL-C and hypertension, amplifying overall cardiovascular risk beyond the sum of individual factors.

According to the 2025 WHO Global Report on Trends in Tobacco Smoking, tobacco use across EU27+UK (age 15+) ranges from 12.5% in the UK to 38.8% in Bulgaria, with an average of 26.0%. This broader measure includes all forms of tobacco use, not just daily cigarette smoking, and therefore captures a more comprehensive and higher burden. Overall, more than one in four adults uses tobacco, making it a significant structural driver of cardiometabolic risk.

High-prevalence countries include Bulgaria (38.8%), Croatia (37.6%), and Cyprus (35.0%), followed by a cluster between 29% and 35% including France, Slovakia, Latvia, Hungary, and Greece. These countries also tend to exhibit elevated levels of other risk factors such as non-HDL cholesterol and blood pressure, confirming that tobacco use acts as a compounding risk amplifier rather than an isolated factor. Bulgaria illustrates this clearly, combining exceedingly high tobacco use with elevated cholesterol, air pollution, and sodium intake, creating a highly adverse cardiovascular risk environment. At the lower end, countries such as the UK (12.5%), Denmark (14.4%), Ireland (17.8%), and Germany (~20%) show more favourable profiles, reflecting stronger tobacco control policies and prevention strategies.

Gender differences are significant but vary by country. On average, tobacco use is higher in men (29.1%) than women (22.8%), but this gap is not consistent. In some countries, particularly Croatia and Bulgaria, female prevalence equals or exceeds male levels, indicating a shift in smoking patterns. This is particularly concerning as increasing tobacco use among women is likely to sustain or increase future CVD burden, given smoking's direct impact on lipid oxidation, endothelial health, and overall atherogenic risk.

France represents a notable case: despite relatively favourable dietary patterns, it has one of the highest tobaccos use rates in Western Europe (34.6%), alongside elevated cholesterol, blood pressure, and CVD prevalence. This highlights the importance of considering tobacco use within a broader, integrated risk framework, as it can offset benefits from other protective factors and contribute significantly to overall cardiovascular burden.

Alcohol Consumption: A Widespread Hypertensive and Hypertriglyceridaemic Risk Factor

Per capita alcohol consumption among adults aged 15 and over, measured in litres of pure alcohol per year for 2019, ranges from 11.3 litres in Greece to 27.3 litres in Romania across the EU27+UK, with an unweighted mean of 17.1 litres. This mean substantially exceeds the WHO-recommended upper limit of 10 litres per capita per year and places the EU27+UK among the highest alcohol-consuming regions globally.

The highest consumption levels are recorded in Romania (27.3 litres), Latvia (21.7 litres), Czechia (21.1 litres), Bulgaria (19.5 litres), Lithuania (19.3 litres), Germany (19.2 litres), Austria (18.8 litres), Poland (18.7 litres), Estonia (18.4 litres), and Ireland (18.1 litres). The lowest levels are observed in Greece (11.3 litres), Italy (12.7 litres), Cyprus (12.7 litres), and Malta (13.0 litres), Southern European and Mediterranean populations whose comparatively moderate alcohol consumption is consistent with their more favourable cardiovascular risk profiles on several dimensions.

The cardiovascular relevance of alcohol in this study operates through two distinct pathways. First, heavy alcohol consumption is a well-established independent cause of hypertension, with each 10 g/day increment in alcohol intake associated with approximately 1 mmHg increase in systolic blood pressure, making alcohol a direct upstream driver of the elevated mean systolic blood pressure values documented in Block 2 of the cardiometabolic marker analysis. In populations such as Romania (27.3 litres per capita), Latvia (21.7 litres), and Lithuania (19.3 litres), which simultaneously record mean male systolic blood pressures of 135.5, 135.7, and 137.3 mmHg respectively, high alcohol consumption represents a plausible contributing mechanism to the observed hypertensive burden. Second, heavy alcohol consumption

elevates fasting triglyceride levels through stimulation of hepatic VLDL synthesis, contributing to hypertriglyceridemia in populations already carrying elevated triglyceride burdens. For the Omega-3 EPA+DHA blood pressure and triglyceride pathways modelled in this study, populations with high alcohol consumption are simultaneously those where the target risk factors, elevated systolic blood pressure and elevated triglycerides, are most likely to be further amplified, reinforcing the case for preventive supplementation in those geographies.

Dietary Patterns: Sodium Excess, Insufficient Plant Food Intake, and Cardiovascular Risk

Dietary patterns data, covering estimated daily intakes of fruit, vegetables, sodium, and sugar-sweetened beverages among adults aged 25 and over for 2019, reveal a nutritional risk landscape that is highly heterogeneous across the study geography and that, in several countries, directly amplifies the cardiometabolic marker burdens documented in the previous section.

Fruits and vegetables consumption, combined as a single indicator against the WHO recommendation of at least 400 g/day for cardiovascular health maintenance, shows that 20 of the 28 countries fall below this threshold. Combined intake ranges from 608 g/day in Greece, the highest in the dataset, to 251 g/day in Czechia. Romania (579 g/day), Italy (461 g/day), Portugal (456 g/day), and Spain (455 g/day) also exceed the threshold. Countries falling most substantially below include Czechia (251 g/day), France (254 g/day), Finland (259 g/day), the UK (273 g/day), Latvia (277 g/day), and Germany (293 g/day). The relatively high intake observed in Southern European countries is consistent with Mediterranean dietary patterns and provides a partial explanation for more favourable lipid profiles, reflecting the contribution of fibre, phytosterols, and polyphenols to cholesterol regulation. Conversely, extremely low fruit intake in Latvia (77 g/day), combined with below-average vegetable consumption, aligns with elevated atherogenic lipid profiles and higher cardiovascular risk observed in earlier sections.

Sodium intake presents a clear and clinically significant risk gradient. The EU27+UK mean stands at 3.7 g/day, substantially exceeding the WHO recommended limit of 2.0 g/day. Ten countries record intakes above 3.5 g/day, with the highest levels in Hungary (5.7 g/day), Bulgaria (5.1 g/day), Croatia (5.1 g/day), Czechia (5.1 g/day), Slovenia (5.1 g/day), Romania (5.1 g/day), Slovakia (5.0 g/day), and Poland (4.4 g/day). The concentration of high sodium intake in Central and Eastern Europe is analytically important, as sodium is a direct driver of elevated blood pressure.

Evidence indicates that each 1 g/day reduction in sodium intake is associated with a 3–5 mmHg reduction in systolic blood pressure.[50] Countries with the highest sodium intake correspond closely with those recording the highest mean systolic blood pressure and prevalence of hypertension. In Hungary, for example, the combination of exceedingly high sodium intake and elevated blood pressure illustrates a direct pathway from dietary exposure to increased cardiovascular risk.

Sugar-sweetened beverage intake, a key contributor to obesity, metabolic dysfunction, and dyslipidaemia, is highest in Malta (217 g/day), Ireland (198 g/day), Luxembourg (186 g/day), Romania (161 g/day), Croatia (160 g/day), and Poland (160 g/day), with the EU27+UK mean at 125 g/day. The distribution does not follow

[50] He FJ et al., Salt Reduction to Prevent Hypertension and Cardiovascular Disease: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(6):632–647

a single regional pattern, indicating the influence of country-specific dietary habits and food environments. The cardiovascular relevance of high sugar-sweetened beverage intake operates primarily through triglyceride elevation, driven by fructose-induced hepatic lipogenesis, and through its contribution to central adiposity and metabolic syndrome, both of which exacerbate atherogenic lipid profiles.

Physical inactivity: Prevalence, Regional Disparities, and Metabolic Consequences

Physical activity data for 2017, measuring the proportion of adults aged 18 and over performing at least 300 minutes of moderate-intensity physical activity outside working hours per week, the level at which cardiovascular health benefits are well-established, show a wide range from 15.9% in Croatia to 83.2% in Estonia, with an EU27+UK mean of 46.3%. This mean implies that most adults across the study geography do not achieve the physical activity level associated with meaningful cardiovascular risk reduction.

The countries with the lowest proportions achieving 300 minutes per week are Croatia (15.9%), Malta (20.3%), Portugal (27.8%), Romania (28.8%), Hungary (29.5%), Belgium (32.8%), and Latvia (34.0%). At the other end of the spectrum, Estonia (83.2%), Slovakia (66.6%), Denmark (66.3%), the Netherlands (65.1%), Sweden (63.9%), Austria (61.3%), and the UK (60.6%) record the highest proportions of physically active adults. The sex differential in physical activity participation is modest at the EU27+UK level, the mean proportion achieving 300 minutes per week is approximately 48.6% among males and 43.8% among females, though the gap widens in specific countries.

Physical inactivity is an independent cardiovascular risk factor operating through multiple biological pathways: it reduces HDL cholesterol, increases LDL-C and triglycerides, contributes to insulin resistance, and elevates blood pressure, precisely the same cardiometabolic markers that define the high-risk cardiovascular profiles documented in the preceding section. The co-occurrence of extremely low physical activity rates in Croatia (15.9%), Romania (28.8%), Hungary (29.5%), and Latvia (34.0%) with their elevated cardiometabolic risk marker burdens and high CVD incidence rates reinforce the compound risk amplification pattern identified throughout this analysis. An adult in Hungary who simultaneously has a mean non-HDL of 3.68 mmol/L, mean systolic blood pressure of 134.9 mmHg, sodium intake of 5.7 g/day, and a physical activity rate placing them in the bottom quartile of the EU27+UK distribution faces a risk environment that is comprehensively and structurally adverse across every modifiable risk factor dimension.

Air Quality: Particulate Matter, Ozone, and the Environmental Dimension of Cardiovascular Risk

Air quality data for 2019 introduce an additional layer to the cardiovascular risk landscape, one that operates independently of individual behaviours yet remains amenable to regulatory and public health action. Annual population-weighted mean PM2.5 concentrations across the EU27+UK range from 5.6 µg/m³ in Finland to 22.6 µg/m³ in Poland, with an overall mean of 12.8 µg/m³. Both the European Environment Agency and the WHO set recommended limits at 5 µg/m³ (2021 guideline) and 10 µg/m³ (previous standard), thresholds exceeded by most countries in the dataset.

The highest PM2.5 concentrations are observed in Poland (22.6 µg/m³), followed by Bulgaria (19.4 µg/m³), Croatia (18.5 µg/m³), Slovakia (18.4 µg/m³), Slovenia (17.0 µg/m³), Czechia (16.8 µg/m³), Hungary (16.5 µg/m³),

Italy (16.1 µg/m³), and Romania (15.7 µg/m³). In contrast, the lowest levels are recorded in Finland (5.6 µg/m³), Sweden (5.7 µg/m³), Estonia (5.9 µg/m³), Ireland (7.8 µg/m³), and Portugal (8.3 µg/m³). This concentration of higher exposure in Central and Eastern Europe reflects structural factors, including greater reliance on coal and biomass for heating, older vehicle fleets, and comparatively less stringent industrial emissions controls.

PM2.5 exposure is a well-established independent cardiovascular risk factor, linked to accelerated atherosclerosis, endothelial dysfunction, systemic inflammation, and increased incidence of acute coronary events and stroke. Epidemiological evidence indicates a 6–13% increase in cardiovascular mortality risk per 10 µg/m³ rise in long-term exposure. Poland exemplifies the compounding effect of environmental and behavioural risks: its PM2.5 levels are more than four times the WHO guideline, coinciding with high smoking prevalence (24.0%), elevated sodium intake (4.4 g/day), high rates of raised blood pressure (28.8%), and increased non-HDL cholesterol (3.67 mmol/L in males). Such clustering reflects broader structural determinants, including socioeconomic conditions and regulatory environments, that shape health outcomes across Central and Eastern Europe.

Seasonal mean ozone concentrations display a distinct geographic pattern, ranging from 28.0 ppb in Ireland to 54.4 ppb in Malta. Southern and Mediterranean countries, including Malta (54.4 ppb), Italy (54.1 ppb), Cyprus (51.8 ppb), and Slovenia (51.4 ppb), record the highest levels, driven by photochemical precursor emissions and higher solar radiation. While ozone is increasingly recognised as an independent contributor to cardiovascular and respiratory morbidity, the available data do not allow for a robust quantitative risk translation without further modelling.

Frost & Sullivan Composite Cardiovascular Risk Index

The epidemiological, cardiometabolic, behavioural, and environmental risk factor data assembled in the previous sections reveal a study geography that is profoundly heterogeneous in its cardiovascular risk burden.

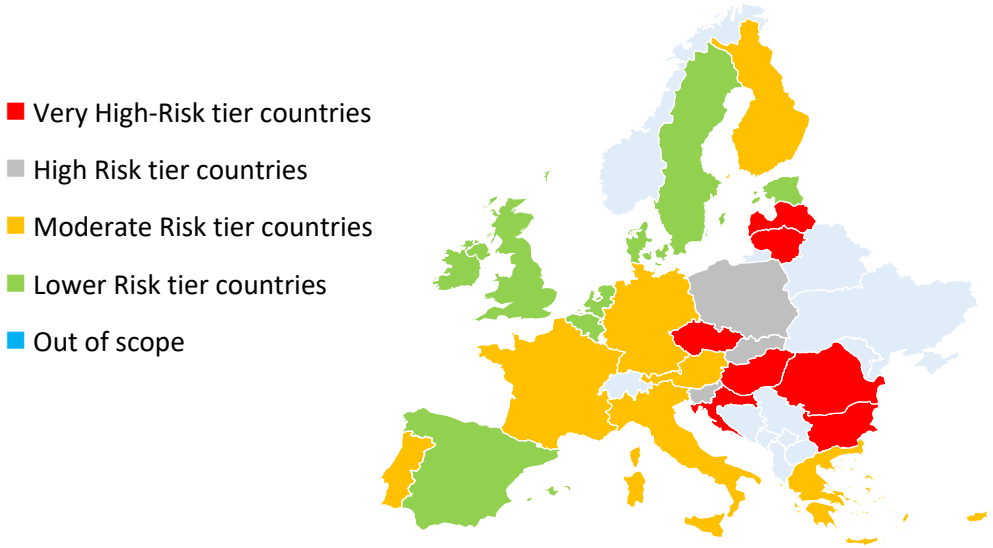

Figure 8.1.4.3: EU27+UK Cardiovascular Risk Index Map

Simply ranking countries by a single indicator, LDL-C, or blood pressure prevalence, or tobacco use in isolation, produces conflicting and unstable hierarchies, because different countries carry their risk burdens through different combinations of upstream factors.

A country with exceedingly high non-HDL cholesterol and elevated raised blood pressure prevalence generates a different absolute event risk profile from a country with moderate lipid burden but exceedingly high sodium intake, obesity, and physical inactivity, and both generate different profiles from a country where tobacco dominates. To resolve this heterogeneity into a single country ranking capable of anchoring the geographic stratification of the cost-savings model, we created a composite cardiovascular risk index synthesising seven independently validated risk indicators into a weighted composite score for each of the 28 countries in the study geography.

The index produced four risk tiers, Very High (score ≥0.65), High (0.50–0.64), Moderate (0.35–0.49), and Lower (<0.35), with seven countries in each tier, producing a clean and balanced stratification across the study geography.

The seven Very High tier countries, Croatia (0.859), Hungary (0.781), Bulgaria (0.742), Czechia (0.711), Latvia (0.711), Lithuania (0.673), and Romania (0.666) are without exception the same countries that recorded the highest CAD and IHD prevalence, the highest stroke incidence, and the most adverse compound cardiometabolic profiles in the epidemiological analysis. They are also the countries recording the lowest male life expectancy in the study geography: Lithuania (71.4 years), Latvia (71.8 years), Bulgaria (72.3 years), Romania (72.6 years), and Hungary (73.9 years) are the five lowest in the dataset, all Very High tier. This three-way alignment between the upstream risk factor index, the observed cardiovascular disease burden, and life expectancy outcomes confirms that the index captures genuine, consequential health burden rather than a statistical artefact of indicator selection.

Croatia retains the highest composite score in the dataset at 0.859, driven by the highest raised blood pressure prevalence (37.3%), the second highest tobacco use (37.6%), the highest physical inactivity rate (84.1% not achieving 300 minutes per week), and very high sodium intake (5.1 g/day) and over-55 obesity (41.9%), an unambiguous and multi-dimensional compound risk profile that no single-indicator approach could adequately capture. Hungary ranks second at 0.781, distinguished by the highest over-55 obesity in the dataset (46.2%), the highest sodium intake (5.7 g/day), the third highest raised blood pressure prevalence (31.5%), and a tobacco burden of 31.5%, a metabolic and dietary risk environment that directly amplifies both the atherogenic lipid and hypertensive pathways. Bulgaria's third place ranking at 0.742 is driven primarily by the highest tobacco use prevalence in the dataset (38.8%) and one of the highest raised blood pressure burdens (29.7%), combined with elevated non-HDL cholesterol (3.78 mmol/L) and high sodium intake.

Romania's position at rank 7 within the Very High tier reflects a distinctive risk profile that differs qualitatively from its Central European peers. Indeed, Romania records the highest alcohol consumption in the entire dataset at 27.3 litres per capita, the only country scoring at maximum on this indicator, combined with extremely high over-55 obesity (43.6%) and physical inactivity (71.2%), and a high-sodium burden (5.1 g/day). Its raised blood pressure prevalence of 15.7% is comparatively low, likely reflecting underdiagnosis in a healthcare system with lower primary care utilisation rates rather than a genuinely

favourable hypertensive environment, and its Very High tier classification is therefore driven by the upstream metabolic and behavioural factors that generate hypertensive and hypertriglyceridaemic risk rather than by the measured blood pressure outcome itself. This distinction is analytically important for the Omega-3 EPA+DHA pathway: Romania's modelled cost savings from blood pressure reduction may be underestimated if the officially measured raised blood pressure prevalence understates the true hypertensive burden.

Several country-level findings in the index are analytically informative precisely because they diverge from what a single-indicator approach would suggest. Greece enters the High risk tier at rank 14 with a score of 0.500, driven by the second highest over-55 obesity in the dataset (43.8%), significant tobacco burden (30.6%), and high physical inactivity (63.8%), a sedentary and metabolic risk profile that the conventional Mediterranean health narrative does not adequately capture and that is consistent with Greece's above-average CAD prevalence in the epidemiological sections. Malta ranks 11th in the High tier through the highest physical inactivity rate among non-Very High tier countries (79.7%) and very high over-55 obesity (41.9%), despite moderate lipid and blood pressure values, a risk profile concentrated in sedentary behaviour and metabolic burden rather than the dietary sodium and atherogenic lipid combination characterising the Eastern European cluster. Estonia, despite carrying significant individual risk factor burdens, ranks 20th in the Moderate tier because its exceptional physical activity rate (83.2% achieving 300 minutes per week) and the lowest sodium intake in the dataset (2.3 g/day) substantively offset other risk dimensions across the composite calculation.

France's Moderate tier classification at rank 15, Germany's Moderate position at rank 18, and the UK's Lower tier at rank 24 are addressed in detail in the methodological commentary that accompanies this index, where the role of national mean averaging, data vintage, and within-country geographic heterogeneity in shaping those rankings is discussed transparently. The core analytical conclusion of the index is not affected by those country-specific considerations: the Very High and High tier countries, concentrated in Central and Eastern Europe and the Baltic states, with High tier extensions into Southern Europe through Greece, Cyprus, Portugal, and Malta, carry a compound cardiovascular risk burden that is structurally and consistently more severe than that of their Western and Northern European counterparts across every layer of the analytical framework.

The index translates this multi-layered burden into a single operational output that serves as the direct analytical foundation for the country-level cost-savings model. The absolute cardiovascular event reduction per thousand supplementation users is highest in the Very High and High tier countries, because those countries combine the highest absolute event incidence rates, documented in the epidemiological sections, with the most adverse modifiable risk factor profiles, the widest treatment gaps documented in the screening and diagnosis sections, and the lowest life expectancy outcomes that together define both the scale of the preventive opportunity and the geographic distribution of populations for whom evidence-based nutritional supplementation provides the most clinically significant and economically consequential complementary risk reduction strategy.

Metabolic & behavioural risk landscape key insights

The cardiovascular disease burden across the EU27+UK is the direct and traceable consequence of a compound upstream risk factor environment whose geographic structure mirrors the mortality and morbidity outcomes documented later in the chapter. Section 1.1.1 characterises this environment across seven dimensions: atherogenic lipid burden, hypertensive load, tobacco use, dietary sodium intake, physical inactivity, obesity in adults over 55, and alcohol consumption, synthesised into a composite cardiovascular risk index that produces the geographic stratification framework used throughout the report.

The geographic concentration of adverse risk profiles is consistent and multi-dimensional. The Baltic and Central European countries record simultaneously elevated non-HDL cholesterol, ranging up to 3.86 mmol/L in Latvia and Lithuania, raised blood pressure prevalence up to 37.3% in Croatia, tobacco burdens reaching 38.8% in Bulgaria, sodium intake up to 5.7 g/day in Hungary, physical inactivity rates up to 84.1% in Croatia, over-55 obesity up to 46.2% in Hungary, and alcohol consumption up to 27.3 litres per capita in Romania. No country in the dataset records an adverse value on any single indicator in isolation, the defining characteristic of the highest-burden countries is the simultaneous co-elevation of multiple risk dimensions.

The composite index, weighting non-HDL cholesterol and raised blood pressure prevalence at 20% each, tobacco and sodium at 15% each, and physical inactivity, over-55 obesity, and alcohol at 10% each, produces four tiers of seven countries. Its validity is confirmed by a three-way alignment with CVD burden data and life expectancy outcomes: the five countries with the lowest male life expectancy in the dataset (Lithuania 71.4 years, Latvia 71.8, Bulgaria 72.3, Romania 72.6, Hungary 73.9) are all Very High tier, and the 7.6-year male life expectancy gap between the Very High and Lower tier means is the most direct human expression of the compound risk burden the index quantifies.

8.1.5 Screening, Diagnosis and Treatment Gaps

This section covers hypercholesterolemia, hypertension, hypertriglyceridemia, cardiovascular risk screening coverage, and the primary versus secondary prevention synthesis collectively and establishes that the cardiovascular prevention system across the EU27+UK fails its highest-risk patients at every stage of the management cascade. This failure is most severe in the populations already identified by the composite risk index as most in need, and the resulting unmet need defines both the scale and the geographic distribution of the preventive opportunity for supplementation.

Hypercholesterolaemia

Despite decades of clinical guideline development and the widespread availability of effective lipid-lowering pharmacotherapy, hypercholesterolaemia remains profoundly undertreated across the EU27 and UK. The gap between recommended and actual clinical practice operates at every stage of the management cascade, from initial screening and risk stratification through to the achievement and maintenance of guideline-recommended LDL-C targets, and is most severe in the Central and Eastern European and Baltic populations that carry the highest compound cardiovascular risk burden documented in the preceding sections of this report.

Systematic cardiovascular risk screening remains inconsistently implemented across the study geography. Countries with structured primary care prevention programmes, notably the UK through the NHS Health Check, the Netherlands, and the Nordic systems, achieve comparatively high rates of lipid testing in the adult population aged 40–74. The majority of EU27 member states, however, rely on opportunistic case-finding rather than systematic screening, with lipid panels measured only when a patient presents for another reason. This structural gap is largest in Central and Eastern European countries, where primary care utilisation rates are lower and a substantial proportion of adults with clinically significant atherogenic lipid burden have never received a fasting lipid test. The case of familial hypercholesterolaemia illustrates the diagnosis gap most acutely: estimated to affect 1 in 250 Europeans, implying approximately 1.8–2.0 million individuals across the EU27+UK, FH diagnosis rates remain below 10% in most member states, with the notable exception of the Netherlands where cascade screening has achieved diagnosis rates approaching 70% of estimated prevalence.[51]

Among patients who have been identified, diagnosed, and initiated on lipid-lowering therapy, goal attainment under current clinical standards is poor. The DAVINCI study, an EU-wide cross-sectional observational study of 4, 112 patients across 18 European countries in primary and secondary care settings, documented that only 18% of very high risk patients achieve the 2019 ESC/EAS LDL-C target of below 1.4 mmol/L.[52] In Central and Eastern European countries specifically, this figure falls to 13%, meaning that 87% of the highest-risk patients in the region most burdened by cardiovascular disease remain above their guideline target despite receiving treatment. Country-level attainment rates against the less stringent 2016 ESC/EAS targets range from 73% in Italy and 72% in the UK to 39% in France, 46% in Germany, and 49% in both Poland and Czechia, countries classified as High or Very High risk in the composite index constructed in this report.[19] The SANTORINI study, conducted in 2020–2021, documents only marginal improvement: overall ASCVD goal attainment stood at 20.7%, representing a 2.7 percentage point increase over the DAVINCI baseline, a near-stagnation that confirms the treatment gap is not primarily a knowledge problem and will not be resolved through guideline publication alone.[53]

The primary versus secondary prevention split reveals where the gap is most clinically consequential. Among primary prevention patients, 59.3% achieve their 2019 LDL-C target, leaving a treatment gap of 40.7%. Among secondary prevention patients, those with established ASCVD and the highest absolute event risk, only 18.5% are at goal, meaning 81.5% remain above target despite confirmed diagnosis and active pharmacological management. Within this secondary prevention population, patients with coronary artery disease record a 2019 goal attainment rate of only 15.4%, and those with cerebrovascular disease 16.1%, the subgroups where inadequate lipid control carries the most immediate mortality consequence,

[51] Vallejo-Vaz et al., Overview of the current status of familial hypercholesterolaemia care in over 60 countries - The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC), Atherosclerosis, 2018 Oct:277:234-255

[52] Ray et al., EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study, *Eur J Prev Cardiol*, 2021

[53] Banach et al., 2022: the year in cardiovascular disease - the year of upfront lipid lowering combination therapy, *Arch Med Sci*, 2022

as confirmed by the REALITY cohort study in Spain, where 24-month all-cause mortality in stroke and peripheral artery disease patients ranged between 10.2% and 11.9%.[54]

The proximate cause of this failure is systematic under-prescription of effective therapy. Fewer than 25% of patients in the SANTORINI study received high-intensity statin therapy, unchanged from the 37–39% documented in the TERCET registry as far back as 2016 and lower than the 38% recorded across Europe in DAVINCI.[20] More critically, 21.4% of ASCVD patients in SANTORINI received no statin at all. Combination therapy, statin plus ezetimibe, was prescribed to only 17.5% of ASCVD patients in SANTORINI, rising marginally from 9% in DAVINCI and from the near-zero rates of 0.3% in myocardial infarction patients documented in the TERCET registry prior to 2016. PCSK9 inhibitor combination therapy, which modelling studies estimate would need to reach 20–22% of high and very high risk patients to achieve guideline goals at population level, was received by only 4.7% in SANTORINI and 1% in DAVINCI, representing a shortfall of approximately 15–17 percentage points against modelled need.[20]

Statin intolerance, frequently cited as a barrier to therapy escalation, does not explain this underperformance at the scale observed. While observational studies report statin intolerance prevalence of 30–40%, true intolerance assessed using validated approved definitions is below 7%, and complete statin intolerance after excluding the drucebo effect[55] falls to approximately 2% of treated patients.[20] Therapeutic inertia, the institutional tendency to maintain patients on suboptimal regimens in the absence of acute deterioration, is the primary driver of the gap between what guidelines recommend and what patients receive.

The geographic concentration of the treatment gap reinforces the risk stratification established earlier in this report. The 87% of very high risk CEE patients not at their LDL-C target, the 61% treatment gap in France, the 51–55% gaps in Germany, Slovakia, Poland, and Czechia, these figures align with the Very High, High, and Moderate risk tier countries of the composite index, with Germany's above-average raised blood pressure prevalence of 26.2% and its Moderate tier classification now correctly reflecting a cardiovascular risk environment that its treatment performance data confirm is more burdensome than its lipid profile alone would suggest. The populations carrying the highest upstream cardiovascular risk burden are simultaneously those receiving the least adequate lipid management, compounding the preventive deficit at every level of the causal chain and defining the geographic distribution of the populations for whom evidence-based adjunctive nutritional supplementation provides the most clinically relevant and economically significant complementary risk reduction opportunity.

Hypertension

The hypertensive burden documented in the cardiometabolic marker analysis, with raised blood pressure prevalence reaching 37.3% in Croatia and mean male systolic blood pressure exceeding 137 mmHg in Slovenia, Lithuania, and Croatia, translates into a cardiovascular prevention imperative only if hypertension

[54] Campuzano R. et al., Assessing LDL-C Levels and Lipid-Modifying Therapies in a Real-World Cohort of Patients with Atherosclerotic Cardiovascular Disease: The REALITY Study, J. Clin. Med. 2025, 14(7), 2340

[55] Drucebo is a combination of DRUg and plaCEBO or noCEBO to relate to beneficial or adverse effects of a drug, which result from expectation and are not pharmacologically caused by the drug

is systematically detected, diagnosed, and treated to target. The evidence from the NCD-RisC global analyses and the SHARE 2021–2022 cohort data establishes that across the EU27+UK the gap between the scale of the hypertensive burden and the adequacy of its clinical management is substantial, geographically structured, and, critically, has plateaued rather than continued to improve over the past decade despite the availability of effective, low-cost antihypertensive medications.

The awareness and detection gap

The first stage of the hypertension management cascade, identifying individuals with elevated blood pressure through screening and primary care contact, remains incomplete across the study geography. The NCD-RisC 2021 pooled analysis of 1,201 population-representative studies covering 104 million participants documented that globally in 2019, 41% of women and 51% of men with hypertension had not received a previous diagnosis.[56] Within Europe, the detection gap is systematically wider in Central and Eastern European countries than in Western and Northern European countries, consistent with the lower primary care utilisation rates and the less developed systematic cardiovascular screening infrastructure documented in those geographies. The SHARE 2021–2022 cohort data, covering 68,047 adults aged 50 and over across 27 European countries, confirm that hypertension diagnosis rates increase substantially with age, from 39.4% of men and 33.5% of women aged 50–64 to 62.6% and 63.1% respectively at ages 65–79, but that Central and Eastern European women aged 50–64 record a diagnosis prevalence of 44.1% compared with 31.2% in Western Europe, a gap of 12.9 percentage points that reflects the higher underlying burden rather than superior detection, since the CEE raised blood pressure prevalence data confirm that a substantially larger share of that population has clinically elevated blood pressure that warrants management.[57]

The clinical significance of undetected hypertension is compounded by the severity distribution of undiagnosed cases. The NCD-RisC 2019 analysis[58] of 12 high-income countries documented that in some age and sex groups in Finland, Italy, and Spain, 15–25% of participants with hypertension had untreated stage 2 hypertension, blood pressure above 160/100 mmHg, without diagnosis or treatment. This is the subgroup where the absolute cardiovascular event risk is highest and where undetected hypertension generates the greatest preventable mortality burden. By contrast, in the best-performing countries, Germany and the UK, this proportion was below 5% in most age groups, reflecting the impact of structured primary care cardiovascular risk assessment programmes on capturing the most severe cases.

[56] NCD Risk Factor Collaboration (NCD-RisC), Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants, Lancet 2021 Sep 11;398(10304):957-980

[57] Grgic and Wazny, Prevalence of hypertension in Europe: a pooled analysis of 68,047 adults from 27 countries Preventive Medicine Reports, Volume 64, April 2026, 103435

[58] NCD Risk Factor Collaboration (NCD-RisC), Long-term and recent trends in hypertension awareness, treatment, and control in 12 high-income countries: an analysis of 123 nationally representative surveys, Lancet. 2019 Aug 24;394(10199):639–651

The treatment initiation gap

Among individuals who have received a hypertension diagnosis, treatment initiation rates across high-income European countries have improved substantially since the 1980s but have plateaued over the past decade.

The NCD-RisC 2021 analysis documents that globally in 2019, 47% of women and 38% of men with hypertension were receiving pharmacological treatment, meaning that more than half of diagnosed women and nearly two thirds of diagnosed men globally remained untreated.

Within the high-income European countries studied, treatment rates by 2017 reached their highest levels in Germany, where the NCD-RisC 2019 analysis identifies treatment coverage approaching 80% in some age groups, and in the UK, which achieved a sharp increase in treatment rates in the late 1990s and early 2000s following the introduction of systematic cardiovascular risk assessment in primary care. At the other end of the European spectrum, Finland, Ireland, and Spain recorded the lowest awareness, treatment, and control rates among the 12 high-income countries studied, findings that are consistent with those countries' lower primary care hypertension management infrastructure and with the country-level raised blood pressure data assembled in this report.

The blood pressure control gap

Even among hypertensive adults who have been both diagnosed and initiated on antihypertensive treatment, blood pressure control, defined as achieving systolic below 140 mmHg and diastolic below 90 mmHg under 2018 ESC/ESH guidelines, remains the most poorly achieved stage of the management cascade. The NCD-RisC 2021 analysis documents global control rates of 23% in women and 18% in men among all people with hypertension in 2019, meaning that most of the global hypertensive population does not achieve blood pressure control. In 2019, control rates above 50% were achieved only in South Korea, Canada, and Iceland, with Germany and Portugal among the highest-performing European countries but still falling short of what structured hypertension programmes demonstrate is achievable.[23]

The NCD-RisC 2019 analysis of 12 high-income countries quantifies the European control ceiling more precisely: even in the best-performing countries among those studied, treatment coverage reached at most 80% and control rates remained below 70% (NCD-RisC, *Lancet*, 2019). At least 20% of diagnosed and treated hypertensive patients across high-income European countries fail to achieve blood pressure control even on pharmacological therapy, a treatment adequacy gap that directly parallels the LDL-C goal attainment gap documented in the preceding hypercholesterolaemia block and that similarly defines a large eligible population for adjunctive non-pharmacological blood pressure reduction.

Critically, control rates plateaued across most high-income countries during the 2000s and have not substantially improved since, suggesting that current pharmacological management strategies have approached their practical ceiling without reaching the level of control that the cardiovascular event reduction evidence base supports as achievable.[25]

Geographic concentration and modelling implications

The hypertension screening, diagnosis, and treatment gap is geographically concentrated in the same Central and Eastern European and Baltic populations that carry the highest compound cardiovascular risk burden in the composite index. The countries with the highest raised blood pressure prevalence, Croatia (37.3%), Latvia (31.7%), Hungary (31.5%), Lithuania (29.9%), and Bulgaria (29.7%), are simultaneously those where primary care cardiovascular screening infrastructure is least developed, where treatment initiation rates are below the European high-income country mean, and where blood pressure control rates are estimated to be among the lowest in the EU27+UK. The compound effect of extremely high hypertensive burden with poor detection and inadequate treatment generates an absolute blood pressure control gap, the number of hypertensive adults not at blood pressure target, which is substantially larger in those geographies than anywhere else in the study.

Hypertriglyceridemia

The hypertriglyceridaemic burden documented in the cardiometabolic marker analysis translates into a clinically important but structurally under-addressed treatment gap across the EU27 and UK. Unlike LDL-cholesterol, triglycerides occupy a structurally subordinate position in routine cardiovascular prevention: they are widely measured as part of standard lipid panels yet are less consistently interpreted as an independent therapeutic target, particularly when LDL-C management dominates clinical decision-making. The result is a management cascade in which hypertriglyceridemia is often detected incidentally, insufficiently investigated for secondary causes, and inadequately treated even in patients with established coronary heart disease and persistently elevated residual risk. This gap is most consequential in the Central and Eastern European and Baltic populations identified in the composite risk index as carrying the highest combined burden of obesity, smoking, raised blood pressure, and other cardiometabolic risk amplifiers, the same risk factor profile that independently predicts undertreated hypertriglyceridemia in the secondary prevention evidence reviewed below.

The first structural barrier to adequate management is definitions inconsistency across clinical frameworks. The 2025 comprehensive review of severe hypertriglyceridemia identified marked heterogeneity across 18 international guidelines: most US guidance defines severe hypertriglyceridemia above 500 mg/dL, while European guidance has historically placed the threshold at above 880 mg/dL, with intermediate ranges variably labelled. The review concludes that this lack of harmonisation directly affects case identification, prevalence estimates, and comparability across health systems, with pooled prevalence of severe hypertriglyceridemia estimated at 1.14% above 500 mg/dL, falling to 0.18–0.19% at higher thresholds, and incidence data described as scarce and inconsistent.[59] While severe hypertriglyceridemia carries a qualitatively distinct risk, including acute pancreatitis, that warrants urgent recognition, the definitional fragmentation it reflects extends downward into mild-to-moderate elevation, where the treatment gap is largest in absolute population terms.

[59] Baass et al., Prevalence, incidence, and definition of severe hypertriglyceridemia: A comprehensive review and weighted summary, *Journal of Clinical Lipidology*, 2025

The screening gap for mild-to-moderate hypertriglyceridemia is therefore not one of complete absence of testing, triglycerides are routinely included in standard lipid panels across Europe, but of under-recognition and inadequate follow-up. Triglyceride elevation is frequently treated as a secondary laboratory abnormality rather than as a marker of remnant lipoprotein burden or residual atherosclerotic risk. Testing conditions compound this: while most studies use fasting samples, routine primary care across much of Europe does not consistently ensure fasting confirmation, which can materially alter case identification. In effect, the screening and diagnosis gap in hypertriglyceridemia is less about whether a blood test was ever performed than whether an abnormal result triggers a structured management pathway, and across most EU27+UK primary care environments, it does not.

The treatment gap in secondary prevention

The treatment gap becomes most visible in secondary prevention populations, where the clinical significance of elevated triglycerides is greatest. The 2025 INTERASPIRE study[60] of 4,069 coronary heart disease patients across 13 countries and six WHO regions found that 33% of patients had hypertriglyceridemia and 24.6% had combined dyslipidaemia despite contemporary lipid-lowering treatment. Only 30% of patients simultaneously achieved both LDL-C below 1.8 mmol/L and triglycerides below 1.7 mmol/L. Approximately four in ten had isolated elevated LDL-C, one in ten had isolated hypertriglyceridemia, and one in four had residual combined dyslipidaemia.

The proximate cause of this failure is not absence of lipid therapy but its narrow concentration on statins alone. In INTERASPIRE, 85% of patients were receiving lipid-modifying therapy and 50% were on high-dose statins, yet only 11.8% were on combination therapy and just 2.3% received specific triglyceride-lowering treatments including fibrates or omega-3 fatty acids. This directly parallels the therapeutic inertia documented in the hypercholesterolemia section: the problem is not lack of guideline awareness but persistent reliance on suboptimal management despite unmistakable evidence of residual risk. The study concludes explicitly that greater use of combination therapy and evidence-based triglyceride-lowering treatments is necessary to reduce the risk associated with residual combined dyslipidaemia.

The risk profile of undertreated hypertriglyceridemia in INTERASPIRE is analytically important for this report's geographic framework as higher triglyceride concentrations were independently associated with smoking, higher BMI, elevated systolic blood pressure, higher LDL-C, lower HDL-C, diabetes, central obesity, and physical inactivity. This risk factor cluster maps precisely onto the Very High- and High-risk tier countries of the Frost &Sullivan Composite Index, Croatia, Hungary, Bulgaria, Czechia, Latvia, Lithuania, Romania, Slovakia, Poland, and Greece, where obesity, insulin resistance, tobacco burden, and hypertension are simultaneously most severe. While country-level hypertriglyceridemia treatment gap data are not available for the full EU27+UK geography, the INTERASPIRE evidence establishes that the

[60] Santos R. et al.,Frequency of residual combined dyslipidemia and hypertriglyceridemia in patients with coronary heart disease in 13 countries across 6 WHO Regions: Results from INTERASPIRE, Atherosclerosis, 2025 Jun:405:119215

populations where residual triglyceride-mediated risk is most likely to remain undertreated after standard statin care are precisely those already prioritised in the composite risk index.

Cardiovascular risk screening coverage

Effective cardiovascular prevention depends on identifying individuals at elevated risk before their first event. The previous section documented that treatment gaps persist even among individuals already identified and initiated on therapy. The more fundamental upstream problem, that a substantial proportion of high-risk individuals have never been systematically assessed, constitutes the most consequential and least quantified gap in the entire management cascade.

Systematic cardiovascular risk assessment using SCORE2, the validated 10-year CVD risk prediction model endorsed by the 2021 ESC prevention guidelines, is unevenly implemented across EU27+UK primary care. Countries with structured national programmes achieve comparatively high coverage: Lithuania's nationwide High Cardiovascular Risk programme screens over 200,000 individuals annually, identifying that 3.2% of over 93,000 middle-aged adults in its electronic database had LDL-C above 6 mmol/L. The majority of EU27 member states, however, rely on opportunistic case-finding rather than systematic risk stratification, with SCORE2 assessments and lipid panels occurring only when a patient presents for another reason.

Evidence from a cross-national SCORE2 and SCORE2-OP cardiovascular risk profiling study covering 24,434 adults undergoing formal risk assessment across Portugal, Italy, Spain, and France quantifies the risk factor burden encountered when structured screening is applied.[61]

Across the combined sample, mean age 60 years, mean systolic blood pressure was 130 mmHg, precisely at the ESC/ESH Stage 1 hypertension boundary above which omega-3 EPA+DHA blood pressure reduction generates its largest absolute effect, as established by the Zhang et al. 2022 dose-response meta-analysis.[6] Within the screened population, 54.9% had systolic blood pressure at or above 130 mmHg and 23.4% at or above 140 mmHg, confirming that more than half of adults aged 50 and over across the 27-country SHARE sample meet the primary blood pressure eligibility criterion for the supplementation intervention modelled in this report.

These findings confirm that when structured cardiovascular risk assessment is systematically applied, clinically actionable risk factor elevation is the rule rather than the exception, and that the failure to screen systematically leaves most of this burden undetected and unmanaged.

Familial hypercholesterolaemia represents the most precisely quantifiable component of the screening gap. Indeed, FH affects approximately 1 in 250 European adults, implying 1.8–2.0 million individuals across the EU27+UK, and generates lifelong atherogenic LDL-C elevation from birth that typically produces coronary artery disease one to two decades earlier than in the general population. Despite this scale, FH diagnosis rates remain critically low across most of the study geography.

The country-by-country analysis by Vallejo-Vaz et al.[18] documents diagnosis rates ranging from approximately 40% in the Netherlands, where government-subsidised cascade screening operated from the

[61] Fontainhas et al., Cardiovascular risk profile with SCORE2 and SCORE2-OP: comparing Portugal, Spain, Italy, and France using the new European predictive models, Front Cardiovasc Med, 2024

1990s until 2014, to below 2% in Croatia, Latvia, and Poland. The diagnostic shortfall is most severe in the countries carrying the highest composite risk index burdens. Croatia has identified approximately 1% of an estimated 15,000 FH individuals, with no identified patient achieving LDL-C below 1.8 mmol/L despite treatment. Latvia has diagnosed 2.3% of estimated cases, with only 5% at LDL-C target before registry inclusion. Bulgaria identified 196 patients from 24,000 screened across 12 cardiology hospitals, with just 5% of very high-risk FH patients at their LDL-C goal. Poland has diagnosed approximately 2% of an estimated 136,300 affected adults. Portugal and France, despite national FH study programmes since 1999 and 2015 respectively, have enrolled below 5% and 3.3% of estimated cases, with fewer than 10% of identified Portuguese patients attaining LDL-C targets.

Even within diagnosed FH populations, goal attainment is inadequate across the study geography: Spain, one of the better-performing systems, reports that only 11% of adult FH patients achieve their LDL-C target despite 80% being on treatment. Countries with the lowest diagnosis rates are simultaneously those where PCSK9 inhibitors, essential for achieving guideline LDL-C targets in FH, remain unreimbursed, and where genetic testing required for cascade screening is patient-funded or unavailable. Lithuania, Latvia, Poland, Ireland, Hungary, and Estonia had not achieved PCSK9 inhibitor reimbursement at the time of the Vallejo-Vaz review.

Primary versus secondary prevention split

The evidence assembled across the four previous sections hypercholesterolemia, hypertension, hypertriglyceridemia, and cardiovascular risk screening coverage, converges on a single analytical conclusion: the treatment gap is not uniformly distributed across the EU27+UK adult population but is systematically most severe in the subpopulation that simultaneously carries the highest absolute cardiovascular event risk. Secondary prevention patients, i.e. those with established atherosclerotic cardiovascular disease, defined as prior myocardial infarction, stroke, coronary revascularisation, or confirmed ASCVD, represent this subpopulation. They are already identified by the healthcare system, already receiving treatment in most cases, and yet remain the furthest from guideline targets across every risk factor dimension examined.

The most direct quantification of this asymmetry comes from the primary versus secondary prevention breakdown of LDL-C goal attainment documented in the treatment gap analysis. Against 2019 ESC/EAS targets, 59.3% of primary prevention patients achieve their LDL-C goal, leaving a treatment gap of 40.7%. Among secondary prevention patients, only 18.5% achieve their goal, a treatment gap of 81.5% that is double the primary prevention shortfall. Within the secondary prevention population, the gap is widest in the highest-risk subgroups: SANTORINI documents goal attainment of only 15.0% in cerebrovascular ASCVD patients and 18.6% in peripheral artery disease patients, the two groups with the highest 24-month mortality documented in the REALITY cohort study. The compound picture is reinforced by INTERASPIRE, which demonstrates that even after a coronary event and within an actively managed secondary prevention population, only 30% of patients simultaneously achieve both LDL-C below 1.8 mmol/L and triglycerides below 1.7 mmol/L, leaving 70% with residual combined dyslipidaemia despite ongoing lipid-lowering therapy.

The blood pressure management gap in secondary prevention follows the same pattern. The NCD-RisC evidence documents that control rates have plateaued below 70% even in the best-performing European systems, and that at least 20% of diagnosed and treated hypertensive patients fail to achieve blood pressure control, a proportion that rises in older, more comorbid secondary prevention populations where polypharmacy, therapeutic inertia, and disease complexity compound the management challenge.

Screening, diagnosis, and treatment gaps key insights

The cardiovascular prevention system across the EU27+UK fails its highest-risk patients at every stage of the management cascade, and this failure is most severe in the populations already carrying the greatest upstream risk burden.

LDL-C goal attainment among very high-risk Central and Eastern European patients stands at only 13% in the DAVINCI study, leaving an 87% treatment gap in precisely the geographies where atherogenic lipid burden is highest. The SANTORINI study documents that only 18.5% of secondary prevention patients achieve their LDL-C target, a treatment gap double that of primary prevention patients. Even among diagnosed and treated hypertensive adults, blood pressure control rates have plateaued below 70% in the best-performing European systems, with at least 20% of treated patients failing to achieve target. Only 2.3% of coronary heart disease patients in INTERASPIRE receive specific triglyceride-lowering therapy despite 33% carrying hypertriglyceridemia. FH diagnosis rates range from 40% in the Netherlands to below 2% in Croatia, Latvia, and Poland. Structured SCORE2-based screening confirms that when systematic cardiovascular risk assessment is applied, more than 70% of assessed adults present with non-HDL cholesterol above guideline thresholds, yet most EU27 member states rely on opportunistic rather than systematic case-finding.

The compound result is that the populations where cardiovascular disease is most severe are simultaneously those receiving the least adequate detection, treatment, and risk factor control.

8.1.6 Life Expectancy at Birth

WHO's life expectancy at birth in 2024 provides the most direct single-metric expression of the cumulative human cost of the cardiovascular risk burden. Across the EU27+UK, male life expectancy ranges from 71.41 years in Lithuania to 81.75 years in Italy, a span of more than ten years within a geography sharing the same clinical guidelines, pharmacological availability, and European health policy framework. Female life expectancy spans from 79.36 years in Bulgaria to 86.44 years in Spain, a difference of 7.1 years. The EU27+UK means stand at 78.1 years for males and 83.5 years for females.

The correspondence between life expectancy and the composite cardiovascular risk index is unambiguous and operates consistently across all four risk tiers. The seven Very High-risk tier countries record a mean male life expectancy of 72.9 years, 7.6 years below the mean of 80.5 years recorded across the seven Lower risk tier countries, and 5.6 years below the seven High risk tier countries at 78.6 years. The gradient is continuous and internally coherent: Moderate tier countries record a mean male life expectancy of 79.6

years, falling between the High and Lower tier means and confirming that the index captures genuine and graded health burden rather than a binary division between high- and low-risk populations.

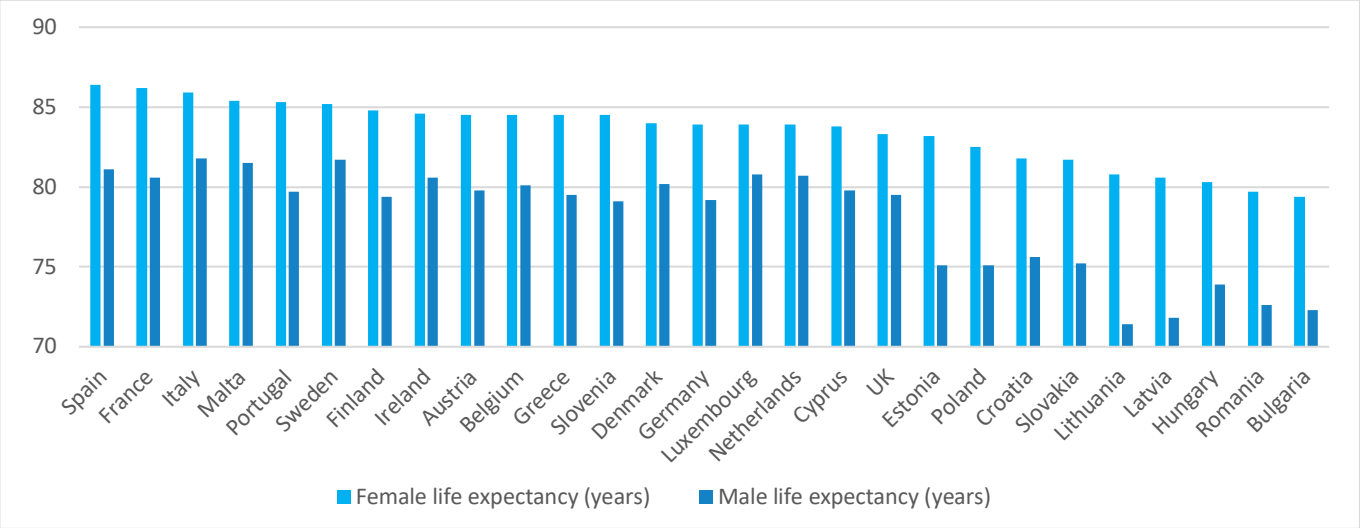

Figure 8.1.6.1: Life expectancy at birth by country and gender in 2024

Five countries record male life expectancies below 75 years: Lithuania (71.4), Latvia (71.8), Bulgaria (72.3), Romania (72.6), and Hungary (73.9). All five are classified as Very High risk. The gap between Lithuania, where the convergence of atherogenic lipid burden, tobacco, physical inactivity, and alcohol consumption is most severe, and Sweden, the highest male life expectancy in the Lower tier at 81.6 years, stands at 10.2 years. A Lithuanian man born today can expect to live a decade less than his Swedish counterpart, and the cardiometabolic and behavioural risk data assembled in this chapter provide a direct mechanistic explanation for that disparity across every indicator in the index.

The High-risk tier shows a notably wider internal spread than the other tiers, reflecting the compositional diversity of its seven members. Poland and Slovakia, whose risk profiles most closely resemble the Eastern European Very High tier in terms of raised blood pressure, sodium, and obesity burden, record male life expectancies of 75.1 and 75.2 years respectively, only marginally above the Very High tier range. At the other end of the High tier, Malta (81.5), Cyprus (79.8), Portugal (79.7), and Greece (79.5) record male life expectancies approaching or equalling Moderate tier levels, consistent with the discussion in the country-specific commentary that their High tier classifications are driven primarily by physical inactivity, obesity, and tobacco burdens rather than by the compound atherogenic and hypertensive profiles that generate the most severe premature male mortality in the Eastern European cluster.

The female-male life expectancy gap adds a further dimension to the risk stratification. The gap is widest in Lithuania (9.4 years), Latvia (8.9 years), Estonia (8.1 years, Moderate tier), Poland (7.4 years, High tier), Romania (7.1 years), and Bulgaria (7.0 years), all either Very High- or High-risk countries. Across the Very High tier as a whole, the mean female-male gap stands at 7.5 years, compared with 5.4 years in the High

tier, 5.4 years in the Moderate tier, and 3.7 years in the Lower tier, a monotonic widening of the sex differential that tracks precisely with the composite risk index and reflects the disproportionate male cardiovascular mortality burden in high-risk countries, driven by the particularly severe male tobacco use, alcohol consumption, and physical inactivity rates documented in the behavioural risk factor analysis. The Lower tier's compressed female-male gap of 3.7 years, ranging from 3.1 years in the Netherlands to 4.4 years in Belgium, reflects both lower absolute male cardiovascular mortality and greater convergence in sex-specific risk factor exposures in those populations.

The female life expectancy data introduce one analytical nuance. Within the Very High tier, female life expectancy (mean 80.4 years) is substantially below female life expectancy in the High tier (83.9 years), the Moderate tier (85.0 years), and the Lower tier (84.2 years), confirming that the Very High tier risk environment is severe for both sexes rather than exclusively male. Bulgaria records the lowest female life expectancy in the entire dataset at 79.4 years, below the male life expectancy of several Western European countries, underscoring the depth of the cardiovascular and all-cause mortality burden in that population. The convergence of Bulgaria's highest tobacco use prevalence in the dataset (38.8%), the third highest raised blood pressure burden (29.7%), and significantly elevated non-HDL cholesterol (3.78 mmol/L) creates a compound risk environment whose consequences are expressed in female as well as male mortality at a level unmatched elsewhere in the study geography.

Taken together, the life expectancy data serve three analytical functions in this report. First, they validate the composite index by confirming that its tier structure maps precisely onto a graded mortality gradient running from 72.9 years mean male life expectancy in the Very High tier to 80.5 years in the Lower tier. Then, they translate the abstract composite scores into human terms, the 7.6-year male life expectancy deficit between the Very High and Lower tier countries represents the most compelling single expression of the cardiovascular burden this study seeks to address. Finally, they provide the demographic context for the cost-savings model: the populations where preventive supplementation generates the largest absolute reduction in cardiovascular events are precisely those where life expectancy is most severely curtailed, where the years of life gained per event prevented are greatest, and where the economic and social returns to effective prevention are correspondingly highest.

8.1.7 Mortality & Morbidity Outcomes

The age-standardised cardiovascular disease mortality rates, premature cardiovascular mortality, and CVD hospitalisation data presented in this section translate the compound risk factor burden and treatment gap evidence assembled throughout this chapter into their most direct human expression. These outcomes are not independent of the previous analysis; they are their consequence.

Across every metric examined, the countries recording the most adverse outcomes are without exception those identified by the composite cardiovascular risk index as carrying the most severe upstream risk factor burden and the widest treatment gaps, confirming the internal coherence of the analytical framework and validating the geographic stratification that underpins the cost-savings model presented in the following chapter.

Age-standardised CVD mortality rates

Age-standardised CVD mortality rates across the EU27+UK in 2023 range from 191.2 deaths per 100,000 in France to 733.1 per 100,000 in Bulgaria, a 3.8-fold differential within a geography sharing the same clinical guidelines, pharmacological availability, and European health policy framework. (see appendix 6.3)

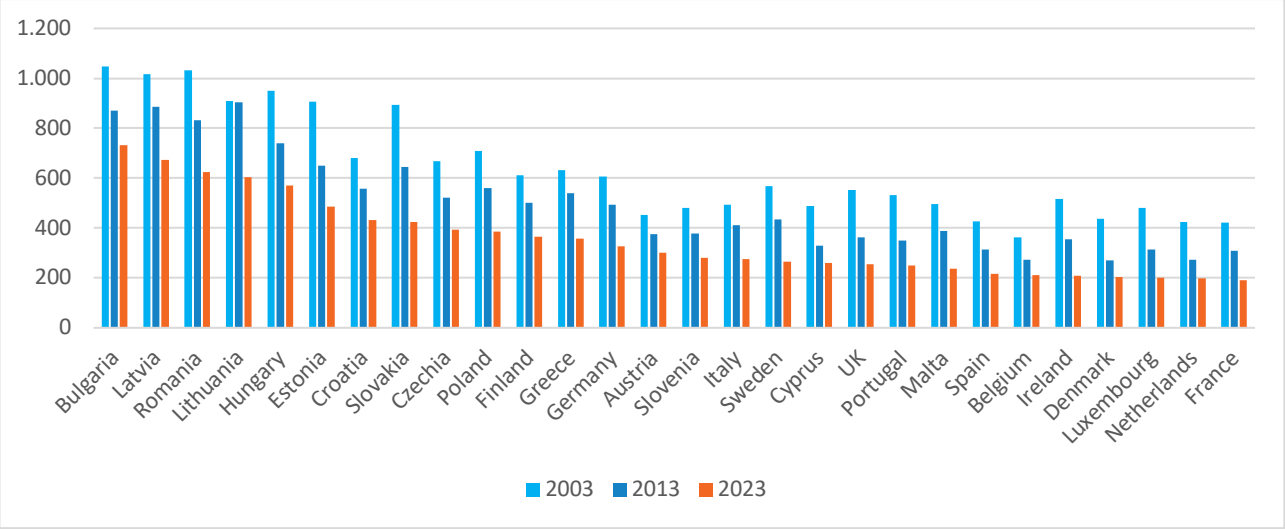

Figure 8.1.7.1 Age-Standardised CVD Mortality Rates, EU27 + UK (2003–2023)

The Very High-risk tier records a mean of 575.5 per 100,000, 2.6 times the Lower tier mean of 220.3, with an absolute gap of 355.1 deaths per 100,000 population. Five countries record age-standardised CVD mortality above 500 per 100,000: Bulgaria (733.1), Latvia (674.1), Romania (623.3), Lithuania (603.4), and Hungary (569.4), all Very High tier. At the other end of the distribution, six countries record mortality below 220 per 100,000: France (191.2), the Netherlands (198.7), Luxembourg (201.9), Denmark (202.8), Ireland (209.6), and Belgium (211.2).

The twenty-year trajectory from 2003 to 2023 shows that every country in the dataset achieved a reduction in age-standardised CVD mortality, but the magnitude diverges sharply along the tier structure. The Lower tier achieved a mean reduction of 53.4% over the period, the Moderate tier 44.9%, the High tier 48.0%, and the Very High tier only 36.4%. Bulgaria recorded the smallest proportional improvement at 30.0%, falling from 1,047.6 per 100,000 in 2003 to 733.1 in 2023, and remains by far the highest-burden country in the EU27+UK. Lithuania presents an analytically important trajectory: between 2003 and 2013 its mortality fell by only 0.5%, from 908.7 to 904.5 per 100,000, effectively stagnant, before declining sharply by 33.3% over the following decade to 603.4 in 2023. This decade of near stagnation followed by accelerated improvement is consistent with delayed benefits from cardiovascular prevention reforms and tobacco policy changes implemented in Lithuania in the early 2010s.

The Very High tier mean reduction of 36.4% over twenty years against 53.4% in the Lower tier confirms that the geographic mortality divide is not closing, the rate of improvement is systematically slowest in the highest-burden countries.

Age and sex-disaggregated cardiovascular mortality

Disaggregating the CVD burden by age group and sex, using 2023 data covering deaths in adults aged 20–54 and adults aged 55 and over, stratified by male and female for all 28 countries, reveals a more granular and analytically important picture than the all-age aggregate statistics alone. The geographic inequality is most extreme in working-age males, most persistent in Very High tier populations of both sexes, and subject to a sex reversal in the oldest age groups that carries direct implications for the supplementation eligible population modelled in this study.

The working-age burden: premature cardiovascular death in adults aged 20 to 54

Working-age cardiovascular mortality, deaths between ages 20 and 54, representing the most economically and socially consequential component of the CVD burden, is concentrated in the Very High- and High-risk tier countries to a degree that exceeds even the all-age mortality differential.

The combined working-age CVD death rate in 2023 ranges from 10.2 per 100,000 in Luxembourg to 93.9 per 100,000 in Bulgaria, a 9.2-fold differential. The Very High tier records a mean working-age CVD death rate of 59.1 per 100,000, compared with 23.9 in the High tier, 19.5 in the Moderate tier, and 13.9 in the Lower tier. The 4.3-fold Very High-to-Lower ratio substantially exceeds the 2.6-fold differential in the all-age data, confirming that the geographic mortality disadvantage falls disproportionately on working-age adults.

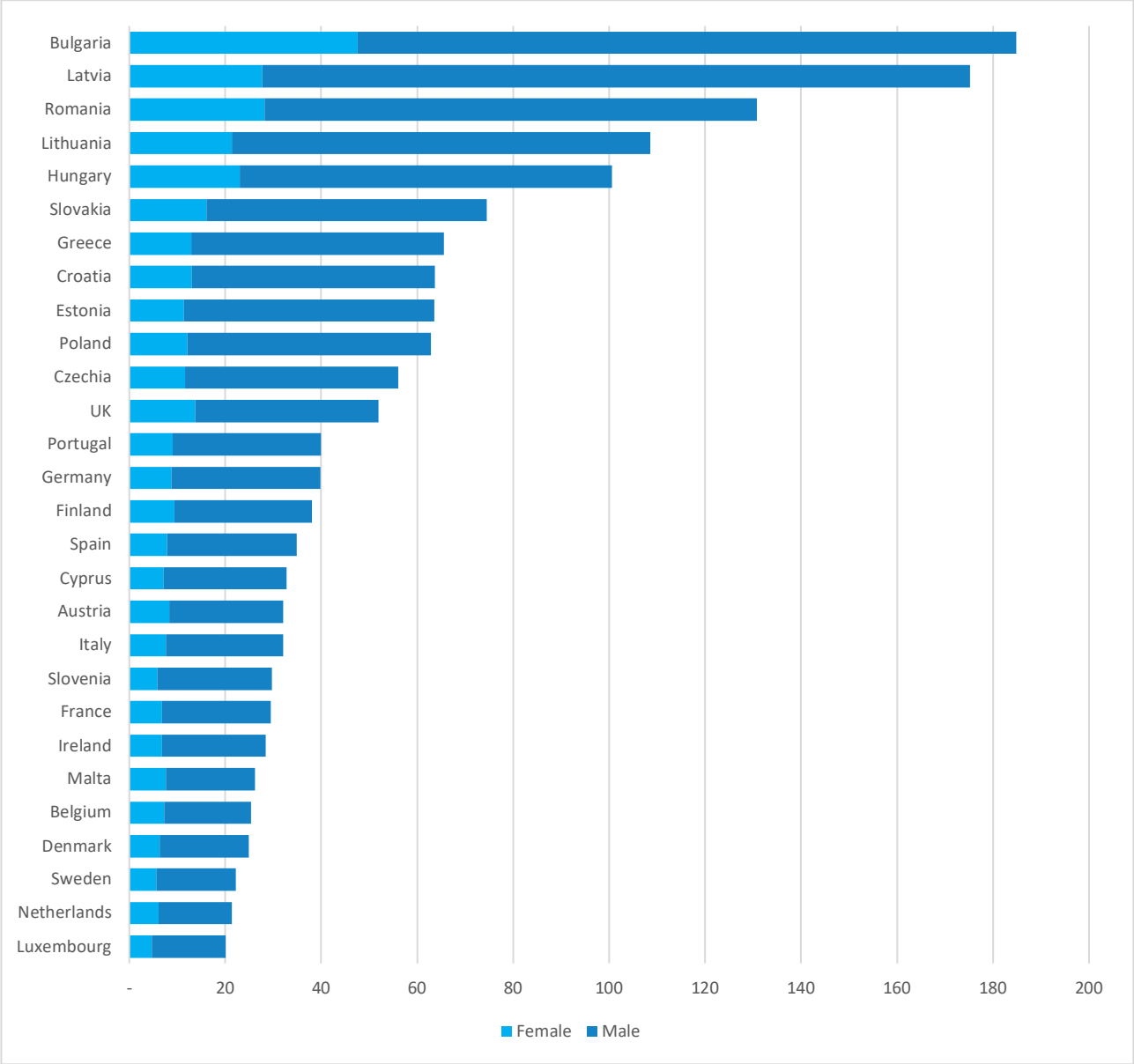

Figure 8.1.7.2: Premature cardiovascular death rate per 100,000 in adults aged 20 to 54 by gender, 2023[10]

Approximately 56,240 adults aged 20–54 die from cardiovascular disease annually across the EU27+UK. The Very High tier accounts for approximately 14,500 of these deaths and the High tier a further 9,800, together 43% of all working-age CVD deaths from a combined population share of approximately 28%. Bulgaria presents the starkest individual case: 33.4% of all Bulgarian CVD deaths occur before age 55, the highest working-age share in the dataset, compared with 11.3% in the Netherlands and 10.9% in Belgium. In Latvia (26.5%), Romania (25.0%), and Hungary (24.9%), more than one in four cardiovascular deaths occurs in a working-age adult. These figures are the direct mortality expression of the compound risk factor burden,

treatment gaps, and healthcare system capacity deficits documented throughout this chapter, operating on populations in the decades of peak economic and family life.

The twenty-year working-age trend reinforces the non-convergence pattern. The Lower tier reduced its working-age CVD death rate by 49.4% between 2003 and 2023, the Moderate tier by 48.7%, the High tier by 42.5%, and the Very High tier by only 33.5%, with the Very High-to-Lower working-age ratio widening from 3.2-fold in 2003 to 4.3-fold in 2023.

The male working-age CVD mortality crisis

The male working-age CVD death rate is substantially higher than the female rate across all 28 countries, with the magnitude of this sex differential varying sharply by geography.

Latvia records the highest working-age male CVD death rate at 147.4 per 100,000, followed by Bulgaria (137.2), Romania (102.6), Lithuania (87.1), and Hungary (77.5). The Very High tier means working-age male rate of 92.4 per 100,000 is 4.5 times the Very High tier means female rate of 24.7. The male-to-female working-age ratio reaches 5.3-fold in Latvia, 4.6-fold in Estonia, 4.2-fold in Poland, and 4.1-fold in Lithuania, Greece, and Slovenia, driven in each case by the particularly severe male tobacco burden, alcohol consumption, physical inactivity, and atherogenic lipid profile documented in the composite risk index.

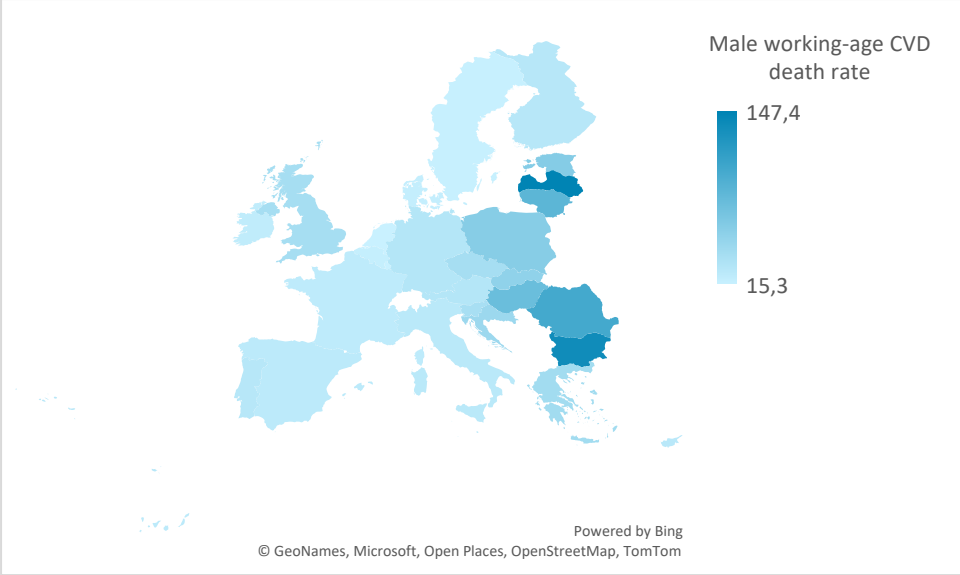

Figure 8.1.7.3: Male working-age CVD death rate[10]

Comparing across geographies rather than within countries reveals the true scale of the working-age male inequality. The working-age male CVD death rate in Latvia (147.4) is 6.5 times the French male rate (22.7) and 9.6 times the Dutch male rate (15.3). The most extreme inequality statistic in the dataset is the 12.8-fold ratio between the Very High tier mean working-age male rate (92.4 per 100,000) and the Lower tier mean working-age female rate (7.2 per 100,000), a figure that simultaneously quantifies the geographic, socioeconomic, and sex-based dimensions of cardiovascular inequality in the EU27+UK.

The female working-age burden, an underestimated inequality

The female working-age CVD death rate tells a geographic story of comparable severity despite lower absolute values.

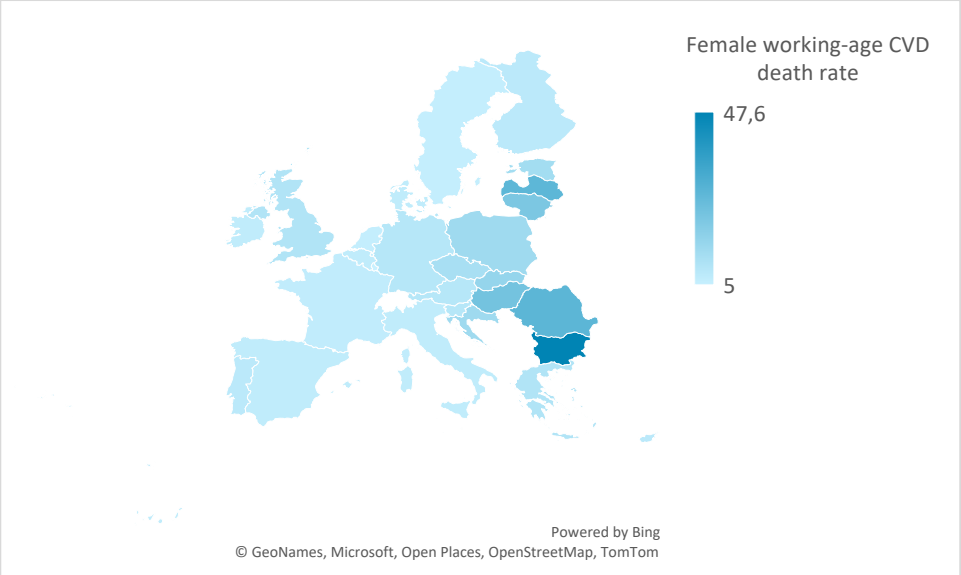

Figure 8.1.7.4: Female working-age CVD death rate

Bulgaria records the highest working-age female CVD death rate at 47.6 per 100,000, 7.0 times the French female rate of 6.8 per 100,000. Romania (28.2), Latvia (27.8), Hungary (23.0), and Lithuania (21.4) follow, all Very High tier. Bulgaria's working-age female rate of 47.6 per 100,000 exceeds the working-age male rates of all seven Lower tier countries, the UK (38.2), Ireland (21.5), Sweden (16.6), Denmark (18.5), Belgium (18.1), the Netherlands (15.3), and Luxembourg (15.4). A working-age woman in Bulgaria faces a higher probability of dying from cardiovascular disease before age 55 than a working-age man in any Lower tier country in the dataset. The Very High tier means female working-age rate of 24.7 per 100,000 is 3.4 times the Lower tier means female rate of 7.2 per 100,000, confirming that geographic inequality overwhelms sex-based differences in risk across national boundaries.

Over-55 cardiovascular mortality and the female burden in older age

Adults aged 55 and over account for approximately 1.75 million CVD deaths annually across the EU27+UK, 97% of the total, and the over-55 data reveal both the sustained geographic inequality and a sex reversal absent from the working-age analysis.

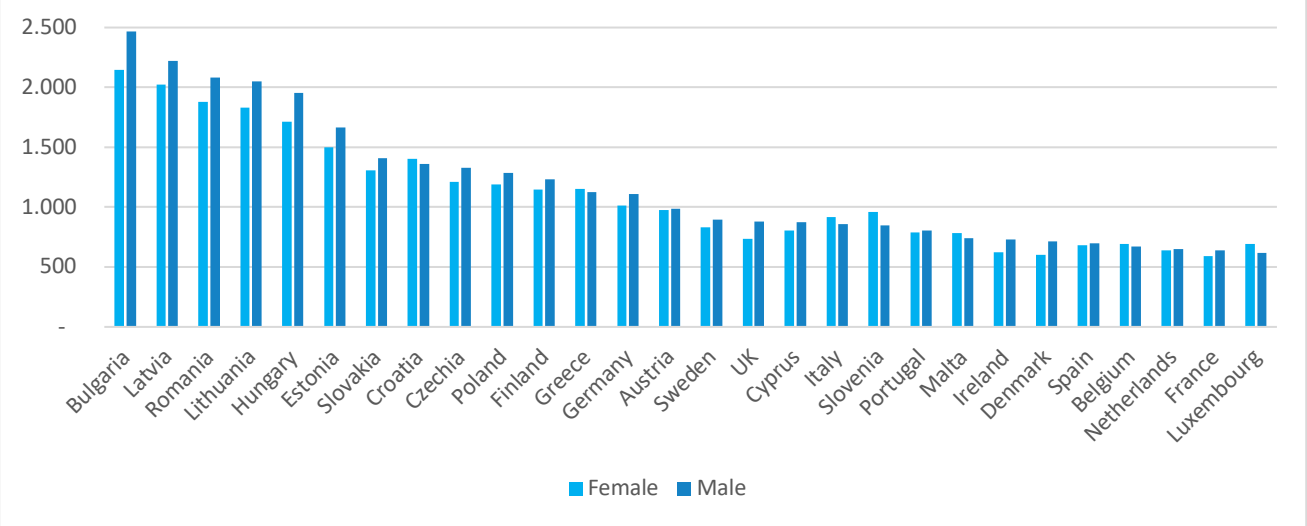

Figure 8.1.7.5: Over-55 cardiovascular mortality rate per 100,000 population in 2023[10]

The Very High tier records mean over-55 CVD death rates of 1,922.8 per 100,000 in males and 1,745.2 per 100,000 in females, against Lower tier means of 736.6 and 687.7 respectively, a 2.6-fold geographic differential for males and a 2.5-fold differential for females. Bulgaria (male 2,466.8, female 2,147.4), Latvia (2,220.6 and 2,024.9), Romania (2,079.9 and 1,880.9), and Lithuania (2,052.6 and 1,833.0) record the four highest over-55 rates for both sexes in the dataset. Seven countries record higher female than male over-55 CVD death rates in 2023: Croatia (female 1,404.7 versus male 1,361.0), Greece (1,150.8 versus 1,126.2), Slovenia (962.2 versus 846.5), Italy (916.2 versus 860.7), Malta (785.7 versus 742.7), Belgium (694.4 versus 668.9), and Luxembourg (692.6 versus 616.5).

This reversal of the working-age male excess reflects the convergence of post-menopausal cardiovascular risk elevation, driven by oestrogen withdrawal, increased arterial stiffness, and sympathetic blood pressure activation, and demographic longevity effects concentrating women in the oldest age groups where cardiovascular disease dominates mortality regardless of sex. The five Very High tier countries with the highest female over-55 CVD death rates, Bulgaria (2,147.4), Latvia (2,024.9), Romania (1,880.9), Lithuania (1,833.0), and Hungary (1,713.9), record female rates exceeding the male rates of every Lower tier country, confirming once more that the geographic inequality overwhelms the sex differential across national boundaries.

Two decades of improvement, and persistent divergence

The twenty-year trajectory from 2003 to 2023 in both all-age and working-age CVD mortality confirms a pattern of universal improvement alongside systematic non-convergence. Every country in the EU27+UK dataset achieved a reduction in age-standardised CVD mortality over the period, a meaningful public health achievement reflecting the cumulative effect of statin availability, hypertension treatment expansion, tobacco control legislation, and emergency cardiac care improvements across the continent.

Yet the rate of improvement is inversely correlated with baseline burden: the countries that needed to improve most improved least, and the geographic mortality divide is wider in proportional terms in 2023 than it was in 2003.

In the all-age age-standardised data, the Lower tier achieved a mean reduction of 53.4% between 2003 and 2023, against 44.9% in the Moderate tier, 48.0% in the High tier, and only 36.4% in the Very High tier. Ireland (59.5%), Luxembourg (57.9%), France (54.7%), and the UK (54.1%) recorded the largest proportional improvements, all Lower or Moderate tier countries that combined already-favourable risk profiles with well-resourced primary care cardiovascular prevention systems. Bulgaria, the highest-burden country in the dataset, achieved the smallest reduction at 30.0%, falling from 1,047.6 per 100,000 in 2003 to 733.1 in 2023, a decline that leaves it with a mortality rate 3.8 times that of France despite two decades of pan-European prevention policy. Latvia (33.6%), Lithuania (33.6%), Croatia (36.7%), and Romania (39.6%) also recorded below-average improvements, all Very High tier countries where upstream risk factor burden, healthcare system capacity constraints, and treatment access gaps have limited the translation of European guideline advances into population-level mortality reduction.

Lithuania presents the most analytically important individual trajectory in the dataset. Between 2003 and 2013 its age-standardised CVD mortality fell by only 0.5%, from 908.7 to 904.5 per 100,000, effectively a decade of stagnation, before declining sharply by 33.3% over the following decade to 603.4 in 2023. This pattern of delayed accelerated improvement is consistent with systemic cardiovascular prevention reforms and tobacco control policies implemented in Lithuania in the early 2010s generating a lagged but substantial mortality benefit, a dynamic with direct relevance to the modelling of intervention timeframes in the cost-savings analysis. It also confirms that structural change within Very High tier health systems is achievable, the challenge is that even Lithuania's improved trajectory has not altered the tier's overall non-convergence with the Lower tier.

In the working-age CVD death rate data, the divergence is even more pronounced. The Lower tier reduced its working-age CVD death rate by 49.4% between 2003 and 2023, the Moderate tier by 48.7%, the High tier by 42.5%, and the Very High tier by only 33.5%. The Very High-to-Lower working-age ratio widened from 3.2-fold in 2003 to 4.3-fold in 2023, meaning that relative to working-age adults in Lower tier countries, adults in Very High tier countries are proportionally more likely to die from cardiovascular disease in 2023 than they were twenty years ago. Greece achieved the smallest working-age CVD mortality improvement in the dataset at 13.3%, followed by Bulgaria (20.9%) and the UK (21.0%). The UK's appearance among the worst working-age performers, despite its Lower tier classification and strong national prevention policy, is consistent with the within-country geographic inequality argument, reflecting the concentrated cardiovascular burden in Scotland, Northern England, and Wales that national averages obscure.

The persistent divergence between tier improvement trajectories over twenty years, across a period that included the 2003 ESC prevention guidelines, the 2019 ESC/EAS dyslipidaemia update, generic statin availability across the EU, mandatory tobacco advertising bans, and successive waves of national cardiovascular prevention programmes, is the strongest analytical argument in this report for the necessity of accessible, non-prescription, population-level preventive interventions. The clinical management frameworks that have driven the substantial improvements documented in the Lower and Moderate tier countries have not translated equivalently into the Very High tier populations where the burden is greatest,

the healthcare system capacity is most constrained, the treatment gaps are widest, and the out-of-pocket financial barriers to pharmacological management are highest.

Nutritional supplementation interventions accessible without prescription and deliverable outside the clinical pathway operate precisely in the gap between what current frameworks achieve and what the epidemiological evidence shows is preventable, and the twenty-year non-convergence documented here defines both the scale of that gap and the urgency of addressing it.

Cardiovascular morbidity and hospitalisation burden

Cardiovascular mortality captures only the fatal endpoint of the disease burden. CVD-specific hospitalisation rates in 2023 provide a complementary morbidity perspective, translating the mortality gradient into acute healthcare utilisation terms and supplying the event-volume denominator required for the cost-savings model.

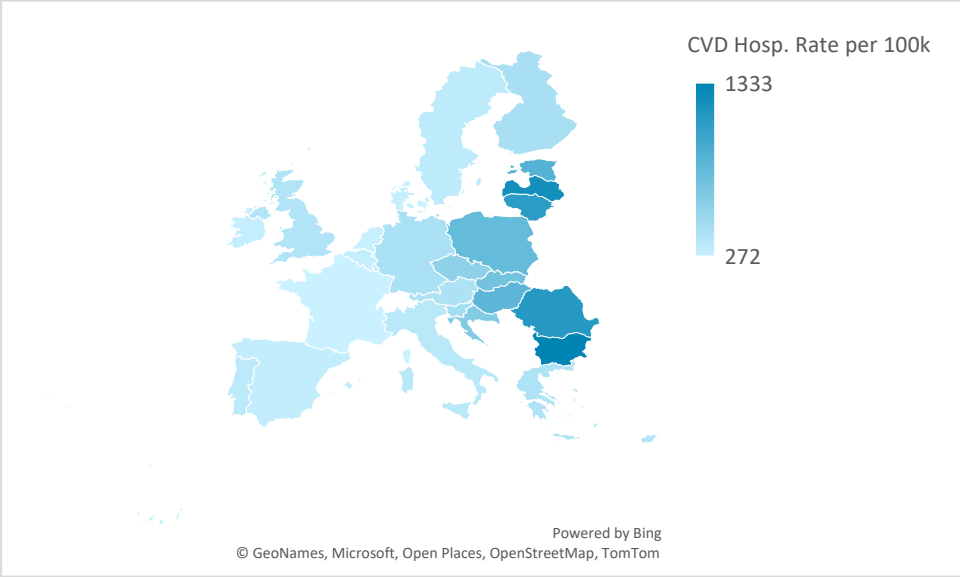

Figure 8.1.7.6: Estimated Cardiovascular Hospitalisation Rates Across Europe (EU27 + UK, 2023)

Estimated CVD hospitalisation rates range from 272 per 100,000 in France to 1,333 per 100,000 in Bulgaria, a 4.9-fold differential.

The Very High tier records a mean hospitalisation rate of 1,015 per 100,000, 3.2 times the Lower tier mean of 319 per 100,000, with four countries recording rates above 1,000: Bulgaria (1,333), Latvia (1,226), Romania (1,132), and Lithuania (1,098), all Very High tier. At the other end of the distribution, five countries record hospitalisation rates below 300 per 100,000: France (272), the Netherlands (282), Luxembourg (287), Denmark (288), and Ireland (298). The High tier mean of 495 per 100,000 and Moderate tier mean of 472 per 100,000 sit broadly in the intermediate range, with Estonia (883) as a notable outlier within the Moderate tier, consistent with its elevated all-age mortality rate relative to its tier classification. Across the EU27+UK as a whole, total estimated CVD hospitalisations stand at approximately 2.4 million annually, of

which the Very High and High tier countries together account for approximately 935,000, 38.7% of the total from a combined population share of approximately 28%.

The hospitalisation data anchor the cost-savings model at the acute event level. The 4.9-fold Bulgaria-to-France hospitalisation differential, applied to Bulgaria's population of 6.5 million, implies approximately 68,000 excess CVD hospitalisations annually relative to the French rate.

Across the Very High tier as a whole, the absolute gap of 696 per 100,000 between the Very High tier mean (1,015) and the Lower tier mean (319), applied to the combined Very High tier population of approximately 48 million, implies approximately 333,000 excess CVD hospitalisations annually above what would be expected at Lower tier rates. This figure represents the aggregate preventable hospitalisation burden that the supplementation cost-savings model targets through triglyceride lowering and blood pressure reduction across the omega-3 EPA+DHA intervention pathway.

Mortality and Morbidity Outcomes Key Insights

Age-standardised CVD mortality in 2023 ranges from 191.2 per 100,000 in France to 733.1 in Bulgaria, a 3.8-fold differential, with the Very High tier mean of 575.5 per 100,000 standing 2.6 times the Lower tier means of 220.3. Five countries record mortality above 500: Bulgaria, Latvia, Romania, Lithuania, and Hungary. The estimated annual toll stands at 1.56 million CVD deaths and 2.4 million hospitalisations across the EU27+UK.

The 20-year trajectory confirms structural non-convergence: Lower tier countries reduced age-standardised mortality by 53.4% between 2003 and 2023 against only 36.4% in the Very High tier. Bulgaria achieved the smallest improvement at 30.0% and remains the most adverse outlier; Lithuania's near stagnation between 2003 and 2013 followed by a sharp 33.3% decline in the subsequent decade illustrates how structural barriers can neutralise prevention policy for an entire national population over an extended period.

Working-age mortality (20–54 years) amplifies the geographic differential to 9.2-fold, with the Very High and High tier countries accounting for 43% of all working-age CVD deaths from 28% of the population. Bulgaria alone records 33.4% of its CVD deaths before age 55. The 12.8-fold ratio between the Very High tier mean working-age male rate and the Lower tier mean working-age female rate is the single most extreme inequality statistic in the dataset. Seven countries record higher female than male over-55 CVD mortality, confirming that the post-menopausal female population constitutes a large and systematically underserved cardiovascular risk group across Southern and Western Europe.

8.1.8 Inequalities in CVD

The cardiovascular risk factor, mortality, and morbidity data assembled throughout this chapter do not describe a randomly distributed burden; they describe a structured inequality rooted in socioeconomic disadvantage, concentrated in specific geographies, expressed differently across sex and age groups, amplified by rural isolation, and compounded by clinical frameworks that were not designed with the most affected populations in mind. The most important analytical finding of this chapter is not any individual statistic but the consistency with which every layer of evidence, from composite risk factor scores to

working-age mortality rates, from FH diagnosis rates to cardiac rehabilitation availability to the clinical trial populations underpinning European guidelines, points to the same countries, the same populations, and the same structural disadvantages.

Cardiovascular inequality in the EU27+UK is not a marginal or incidental feature of the health landscape. It is its dominant characteristic.

The geographic divide: East versus West

The most striking cardiovascular inequality across Europe is the persistent geographic divide between Central and Eastern European and Baltic countries and their Western and Northern counterparts. This divide is not a gradual gradient but a structural discontinuity, broadly aligned with the former Iron Curtain, which remains visible across all indicators and has narrowed only modestly despite two decades of coordinated prevention efforts.

At its core lies a markedly different upstream risk environment. In Very High-risk countries, including Bulgaria, Romania, Latvia, Lithuania, Hungary, and Czechia, cardiovascular risk factors do not occur in isolation but cluster simultaneously. Elevated cholesterol, hypertension, smoking, high sodium intake, physical inactivity, obesity, and alcohol consumption co-exist within the same populations. This contrasts with Western Europe, where adverse risk factors tend to be more isolated and better managed. The result is not simply higher risk, but a qualitatively different and more complex burden, compounded by comparatively weaker health system capacity to detect and manage disease.

The mortality impact is substantial. In 2023, age-standardised CVD mortality ranged from around 190 per 100,000 in France to over 730 in Bulgaria, representing a nearly fourfold difference within a region governed by shared clinical guidelines. On average, Very High-risk countries record mortality rates more than twice those of Lower-risk countries. This translates into significant differences in life expectancy, with men in the highest-risk countries living, on average, over seven years less than their Western European counterparts. Importantly, this divide is not closing. Between 2003 and 2023, mortality reductions were significantly greater in lower-risk countries than in higher-risk ones, meaning relative disparities have widened over time. In some cases, progress has been particularly slow, reflecting structural barriers to translating clinical advances into population-level outcomes.

These inequalities are reinforced across the entire prevention and treatment cascade. Rates of LDL cholesterol control, familial hypercholesterolaemia diagnosis and access to cardiac rehabilitation are consistently lower in Central and Eastern Europe. Taken together, these gaps point to a systemic issue: cardiovascular inequality in Europe is not driven by a single factor, but by the cumulative effect of risk exposure and sustained underinvestment across the full continuum of care.

The rural dimension, geography within geography

The East-West divide is compounded by a within-country rural-urban gradient that national averages systematically obscure. Eurostat urban-rural typology data at NUTS regional level (2021) reveal that the

Very High and High tier countries of Central and Eastern Europe are overwhelmingly characterised by predominantly rural and intermediate regions at subnational scale.[62] Romania, Bulgaria, Lithuania, Latvia, Croatia, Poland, and Slovakia are dominated by green and brown regions in the Eurostat choropleth map, vast predominantly rural and intermediate hinterlands surrounding small urban clusters concentrated at the capitals.

By contrast, Belgium, the Netherlands, Luxembourg, Denmark, and much of the UK are predominantly urban and suburban, with blue regions covering most of their territory. The population distribution bar charts confirm that Very High tier countries have substantially higher rural population shares than Lower tier countries at national level, translating the regional visual pattern into a quantitative national summary.

This rural concentration matters for cardiovascular prevention because rural populations in Eastern Europe face compounded disadvantage across every dimension of the management cascade. They record higher rates of tobacco use, physical inactivity, and adverse dietary patterns than urban populations in the same countries; they have lower rates of hypertension diagnosis, lipid screening, and structured cardiovascular risk assessment; they live further from the lipid clinics, cath labs, cardiac rehabilitation programs, and specialist cardiology services concentrated in capital city clusters; and they are disproportionately represented in the lowest income quintiles of countries with already high Gini coefficients, meaning they face the greatest out-of-pocket financial barriers simultaneously with the lowest proximity to care.

The national average statistics for CVD mortality, hospitalisation, and treatment gap in Very High tier countries therefore understate the true burden experienced by most of their populations who live outside the urban centres. The cardiovascular inequality between Eastern and Western Europe is in practice larger than country-level comparisons suggest, because the Eastern European populations exposed to the worst risk factor environments and the least adequate healthcare access are disproportionately rural, and their outcomes are diluted by the comparatively more favourable profiles of the urban minorities in the same country averages.

Gender differences, two distinct burdens, one shared failure

The cardiovascular inequality observed across Europe has a distinct sex-specific dimension that goes beyond the traditional narrative of male excess risk. The 2023 data reveal two parallel and structurally different patterns: a severe working-age male mortality crisis concentrated in Eastern Europe, and a substantial but often under-recognised burden among older women across all regions. Together, these highlight systemic gaps in how cardiovascular risk is identified and managed.

Among working-age populations, the disparity is most acute in Very High-risk countries. Male CVD mortality reaches exceptionally elevated levels, 147 per 100,000 in Latvia and over 100 in Romania, far exceeding Western European counterparts. These differences reflect the clustering of behavioural and metabolic risk factors, including smoking, alcohol consumption, and dyslipidaemia. The resulting male-to-female mortality ratios, exceeding fivefold in some countries, represent the most extreme inequality observed. However,

[62] Eurostat urban-rural typology data at NUTS regional level (2021)

these framing obscures an equally important insight: female mortality in these same countries is also elevated. In Bulgaria, for example, female working-age mortality exceeds male rates in all Lower-tier countries, indicating that geographic inequality can outweigh biological sex differences.

In older populations, the pattern shifts. In several countries, including Italy, Greece, and Belgium, female mortality surpasses male mortality. This reflects both biological changes associated with menopause, such as increased blood pressure and vascular stiffness, and demographic factors, with women disproportionately represented in older age groups. Evidence from SHARE data shows particularly high rates of hypertension among older women in Central and Eastern Europe, often exceeding male prevalence. Despite this, female cardiovascular risk remains underdiagnosed and undertreated.

A key driver of these disparities lies in the clinical evidence base. Analyses of ESC guideline references show that women are significantly underrepresented in cardiovascular research, and sex-specific considerations are largely absent from recommendations. As a result, current clinical frameworks insufficiently address female risk profiles.

Overall, both working-age men in high-burden regions and older women across Europe represent populations inadequately served by existing prevention and treatment paradigms, pointing to the need for more tailored, sex-informed approaches.

Socioeconomic disparities, the financial architecture of cardiovascular disadvantage[63]

The geographic and gender inequalities documented in this report are underwritten by a socioeconomic gradient of comparable magnitude that provides their structural cause and limits the effectiveness of conventional prevention frameworks in addressing them.

The most direct expression of this gradient is in healthcare investment. Health expenditure per capita in purchasing power parity terms across the Very High tier averages €2,831, less than half the Lower tier mean of €6,486 and less than 40% of Germany's €7,143 or Luxembourg's €7,163. Romania records the lowest health expenditure per capita in the dataset at €2,248, less than a third of Germany's, yet simultaneously the third highest CVD mortality at 623.3 per 100,000. Bulgaria (€2,554), Hungary (€2,473), Latvia (€2,609), and Croatia (€2,777) are clustered at similarly low investment levels against the highest cardiovascular mortality rates in the study geography. The resource-to-burden inversion is the defining feature of cardiovascular socioeconomic inequality in the EU27+UK: Germany spends 3.2 times more per capita than Romania on healthcare and records mortality 1.9 times lower, a compound disadvantage of lower investment generating worse outcomes that would require even greater investment to address.

Czechia represents an analytically important exception within the Very High tier. At €3,870 per capita, substantially higher than its Very High tier peers and closer to Moderate tier levels, Czechia demonstrates that elevated health expenditure alone cannot resolve cardiovascular mortality disadvantage when the upstream risk factor burden remains severe. Its mortality rate of 393.3 per 100,000 confirms that the compound atherogenic, dietary sodium, and physical inactivity burden documented in the composite risk

[63] All datapoints in this section are coming from the World Bank

index generates persistent cardiovascular mortality regardless of comparatively greater healthcare investment. Equally instructive, Czechia's out-of-pocket share of 14.6%, the second lowest in the Very High tier, suggests that where public financing is more comprehensive, financial access barriers are meaningfully reduced even within a high-burden country.

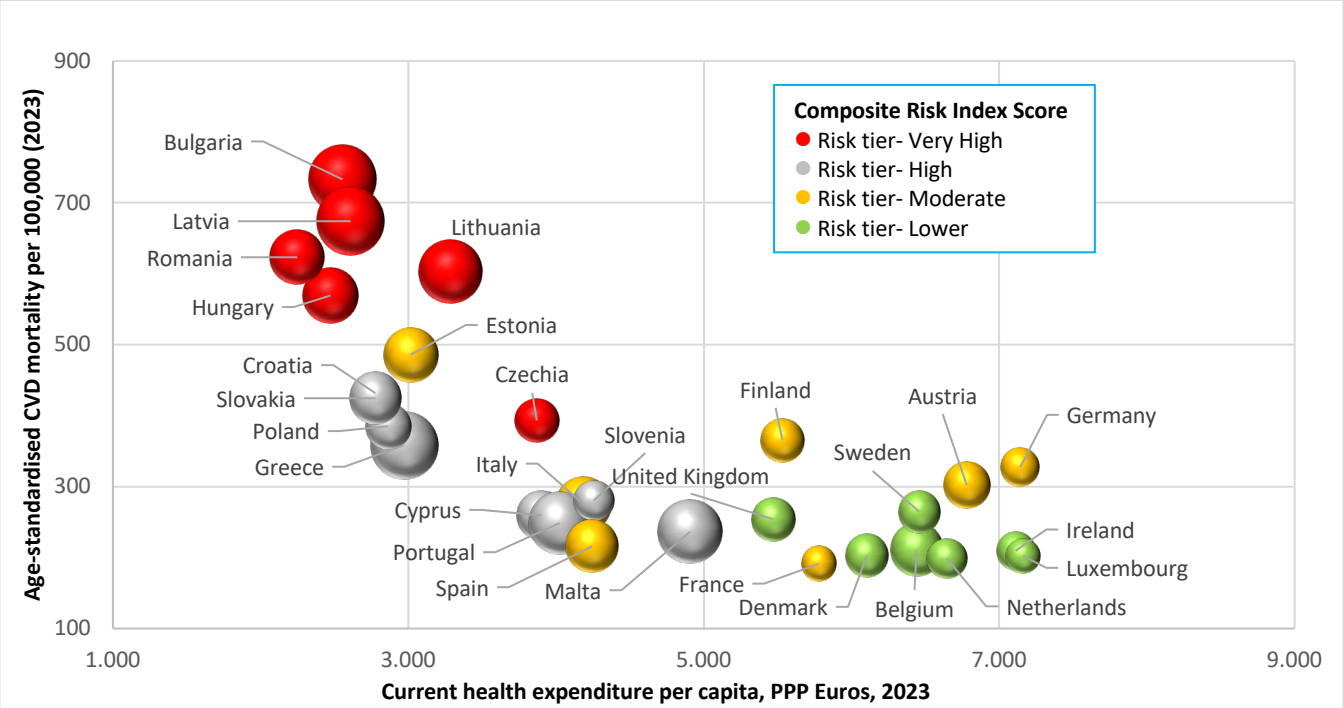

Figure 8.1.8.1: The Socioeconomic Architecture of Cardiovascular Inequality, EU27+UK, 2023
X-axis: Health expenditure per capita (PPP, current international €)
Y-axis: Age-standardised CVD mortality per 100,000
Bubble size: Out-of-pocket private health expenditure as % of total health spending
Colour: Composite cardiovascular risk index tier

Out-of-pocket healthcare expenditure is the variable that most sharply predicts treatment access barriers independent of total spending. Bulgaria (35.5%), Latvia (35.1%), Greece (34.3%), Lithuania (31.0%), and Malta (30.9%) record the highest private expenditure shares in the dataset, meaning that between a third and two fifths of all healthcare costs fall directly on patients. In Bulgaria and Latvia this combines with the lowest total health expenditure in the Very High tier and Gini coefficients of 40.5 and 35.7 respectively, creating a catastrophic affordability barrier for lower-income patients seeking lipid-lowering therapy, antihypertensive management, and specialist cardiovascular care. Greece's 34.3% OOP share, the highest in the dataset, is particularly anomalous given its High rather than Very High tier classification, illustrating that high private cost burden operates as a treatment access barrier independently of national risk tier: a well-resourced specialist cardiology infrastructure is effectively inaccessible to lower-income patients who cannot afford private care.

The direct consequence is visible across every treatment metric: 13% LDL-C goal attainment in very high-risk CEE patients, single-digit FH diagnosis rates in Croatia and Latvia, and PCSK9 inhibitor access restricted

to private funding in Lithuania and Latvia despite those countries recording some of the highest CVD mortality rates in the dataset. Financial barriers to cardiovascular care are not a peripheral concern in the EU27+UK, they are a primary driver of the mortality and morbidity inequality this report documents.

Cardiovascular inequalities key insight

The geographic, rural, gender, and socioeconomic dimensions of cardiovascular inequality documented in this section converge on a single analytical conclusion. The populations carrying the highest cardiovascular disease burden in the EU27+UK are the same populations where the treatment gap is widest, the healthcare system is least resourced, the financial barriers to pharmacological management are greatest, the clinical evidence base is least applicable, and the upstream risk factor environment is most severe. These are not independently distributed disadvantages, they are structurally co-located in the same geographies, the same demographic groups, and the same socioeconomic strata. The result is that the preventive opportunity for supplementation interventions is not uniformly distributed across the EU27+UK but is concentrated and compounded in exactly the populations that current clinical management frameworks have proven least able to reach equitably. The cost-savings model presented in the following chapter is built on this concentration, weighting its outputs to reflect where absolute event rates are highest, where treatment gaps are widest, and where each prevented hospitalisation or death generates the greatest human and economic return.

8.2 The Economic Burden of CVD in the EU27+UK

The epidemiological evidence assembled in the previous sections establishes that CVD imposes a profound and geographically concentrated disease burden across the EU27+UK, 1.56 million deaths, 2.4 million hospitalisations, and approximately 925,000 new cases annually.

These figures are not merely clinical statistics. Each death, each hospitalisation, and each new case entering the CVD pipeline generates measurable economic consequences: direct expenditures on acute care, pharmaceutical management, and rehabilitation; indirect costs from lost productivity, premature exit from the labour market, and informal caregiving; and longer-term fiscal pressures on health systems whose capacity is already mismatched to the populations carrying the greatest burden.

This section quantifies the scale of those consequences across the EU27+UK, disaggregates them by cost category and geographic tier, and situates them within the demographic and epidemiological trajectory that will determine their future magnitude. Taken together, the evidence presented here makes the economic case for prevention that the supplementation cost-savings model in a following section, then translates into quantified intervention returns.

8.2.1 Scale of the Economic Burden

Cardiovascular disease is the single largest contributor to healthcare expenditure across the European Union.[64] The most comprehensive population-based cost study of CVD in the EU, published in the European Heart Journal in 2023 by Luengo-Fernandez and colleagues, estimates the total annual societal cost of CVD across the 27 European Union member states at €282 billion, of which approximately €155 billion represents direct health and social care costs, equivalent to 11% of total EU health expenditure, with the remaining €127 billion reflecting indirect costs from productivity losses due to premature mortality and morbidity-related work incapacity, and from informal caregiving by family members and unpaid carers.

This study covers the EU27 only, as the UK had left the European Union before the 2021 reference year. An indicative UK estimate of approximately €28.5 billion is available from Wilkins et al., sourced from the same Oxford Health Economics Research Centre team using an equivalent cost-of-illness framework applied to 2015 data, subsequently adjusted to approximate 2021 euros using EU HICP cumulative inflation of 9.5% for the period. This figure is not directly comparable with the Luengo-Fernandez EU27 estimate due to the difference in reference year and the methodological advances incorporated in the 2023 study, in particular the integration of SHARE individual patient-level data for informal care estimation and is therefore presented as an indicative contribution rather than a comparable data point. On this basis, the combined EU27+UK annual societal cost of CVD is estimated at approximately €310 billion, a figure used throughout this report as the geographic scope headline where EU27+UK coverage is stated.

The €282 billion EU27 estimate is grounded in 2021 cost and utilisation data and should be understood as a conservative floor rather than a current ceiling: the 2023 epidemiological evidence assembled in Section 1.1.1, combined with healthcare cost inflation across EU Member States and the continued demographic ageing of the study population, implies that the true current burden is materially higher. The estimate nonetheless provides the most methodologically robust and geographically comprehensive macro-anchor available for the EU27 context and is used as such throughout this chapter.

To situate the scale of this burden, €282 billion exceeds the total annual GDP of countries such as Portugal or Romania, and the direct cost component alone, approximately €155 billion, is equivalent to the combined annual health budgets of the ten smallest EU Member States. Since 2003, when the comparable estimate stood at €169 billion, the total burden has grown by €113 billion in nominal terms, a 67% increase over two decades that reflects the compounding effect of demographic ageing, rising treatment costs, and the persistent failure of preventive frameworks to reduce incidence at the rate required to offset population growth in high-risk age groups.[31,65,66,67]

The direct cost component is driven by four categories of expenditure. Acute hospitalisation for cardiovascular events, myocardial infarction, stroke, and decompensated heart failure, represents the single largest cost driver, accounting for €79 billion and the majority of direct spending in most EU health

[64] Luengo-Fernandez et Al., Eur Heart J. 2023 Dec 1;44(45):4752-4767

[65] Wilkins et al. (2017), European Cardiovascular Disease Statistics 2017. European Heart Network, Brussels

[66] Leal J, et Al. European Heart Journal 2006;27(13):1610–1619

[67] OECD. The State of Cardiovascular Health in the European Union. OECD Publishing, Paris, 2025

systems.[31] Long-term pharmaceutical management, primarily statins, antihypertensives, and anticoagulants, constitutes the second largest category at €31 billion, reflecting the chronic and relapsing nature of established cardiovascular disease. Revascularisation procedures, percutaneous coronary intervention and coronary artery bypass grafting, generate high per-procedure costs concentrated in secondary and tertiary care settings. Cardiac rehabilitation and post-event follow-up round out the direct cost picture, though these are systematically underinvested in across the Very High- and High-risk tier countries where the event burden is most concentrated, as documented in the screening and treatment gap analysis in Section 6.1.

The geographic distribution of this burden does not reflect the geographic distribution of EU population or GDP. The Very High-risk tier countries, Bulgaria, Croatia, Hungary, Latvia, Lithuania, Romania, and Slovakia, account for a disproportionate share of the absolute event volume that drives direct costs. Their mean age-standardised CVD mortality of 295.2 per 100,000 is 3.6 times the Lower tier means of 81.6, and their estimated CVD hospitalisation rate of 1,015 per 100,000 is 3.2 times the Lower tier means of 319. Yet health expenditure per capita in purchasing power parity terms across the Very High tier averages only €3,460, compared to €6,489 across western EU comparators.[68]

The result is a resource-to-burden inversion that is the defining structural feature of CVD economics across the EU27+UK: the countries generating the highest absolute event volumes and therefore the highest intrinsic cost burden are simultaneously the countries with the least financial capacity to absorb or address that burden through conventional clinical management pathways. This inversion has direct implications for how the economic burden should be interpreted and how the preventive opportunity should be valued. A healthcare cost saving achieved in Bulgaria or Romania through reduced CVD hospitalisation does not only free up marginal budget capacity, but it also relieves pressure on a system operating at or near its resource ceiling, where each prevented hospitalisation carries a proportionally larger system-level impact than the equivalent event prevented in a well-resourced western European health system.

The cost-savings model presented in Section 5 reflects this asymmetry by weighting its geographic outputs to the incidence and hospitalisation rates documented throughout this chapter, ensuring that the estimated savings capture the full value of prevention in the populations where it matters most.

8.2.2 Direct Healthcare Costs

Direct healthcare costs represent the most immediately quantifiable dimension of the CVD economic burden and the component most directly addressable through preventive intervention.

Across the EU27+UK, direct healthcare costs collectively account for approximately €155 billion annually, equivalent to 11% of total EU health expenditure, encompassing acute inpatient care for cardiovascular events, long-term pharmaceutical management, revascularisation and surgical intervention, and cardiac rehabilitation. The distribution of these costs across the 28 geographies is not proportional to population

[68] Eurostat 2024, Purchasing power parities indicator

size, GDP, or healthcare investment. It is determined by the same compound risk factor burden and treatment gap structure documented throughout section 2.1, and it concentrates the greatest absolute event volumes in the countries with the least financial capacity to absorb them.

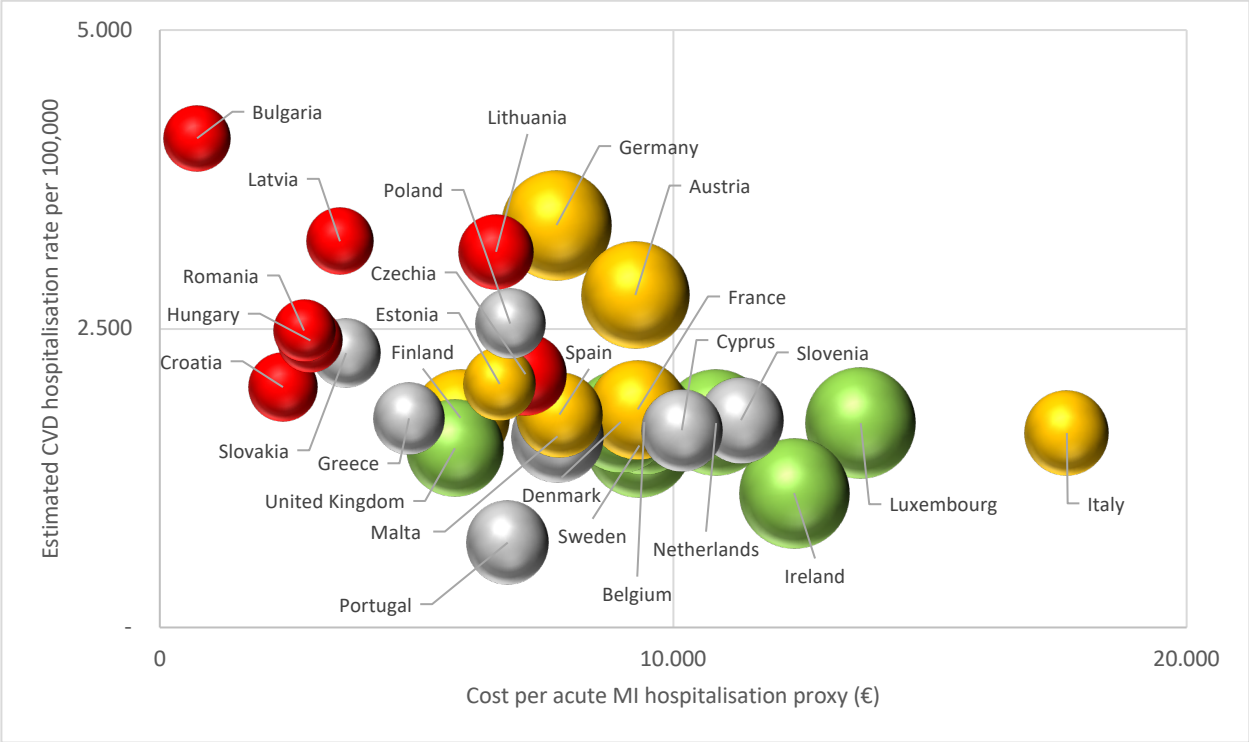

Figure 8.2.1: Burden vs. Cost: MI Hospitalisation Expenditure Across CVD Risk Tiers

Acute hospitalisation

Acute hospitalisation is the dominant cost driver within the direct cost envelope, and the per-case cost differential across the EU27+UK is as analytically significant as the event-volume differential. The cost of an acute myocardial infarction hospitalisation ranges from €726 in Bulgaria to €17,667 in Italy, with the Very High-risk tier recording a mean of approximately €3,874 per acute MI admission against a Lower tier mean of approximately €10,102.

This 2.6-fold cost inversion, which precisely mirrors the all-age CVD mortality differential between the same tier groupings documented in section 2.1.7, reflects the compounding effect of lower procedural complexity, shorter inpatient stays, more limited access to interventional cardiology infrastructure, and systematically lower DRG[69] tariff levels in Central and Eastern European health systems. Ireland (€12,354), Luxembourg (€13,652), Slovenia (€11,320), and the Netherlands (€10,836) record the highest MI

[69] Hospital care costs are valued using country-specific diagnosis-related group (DRG) tariffs, standardised reimbursement rates that assign a fixed payment to each inpatient admission based on its primary diagnosis and expected resource use.

hospitalisation costs, while Romania (€2,810), Hungary (€2,933), Croatia (€2,399), and Bulgaria (€726) record the lowest. The implication for the aggregate direct cost burden is counterintuitive but analytically important: the countries generating the highest absolute MI event volumes, Bulgaria with an estimated hospitalisation rate of 1,333 per 100,000 and Romania at 1,132 per 100,000 against the EU27+UK mean of approximately 580, are simultaneously the countries incurring the lowest per-case costs.

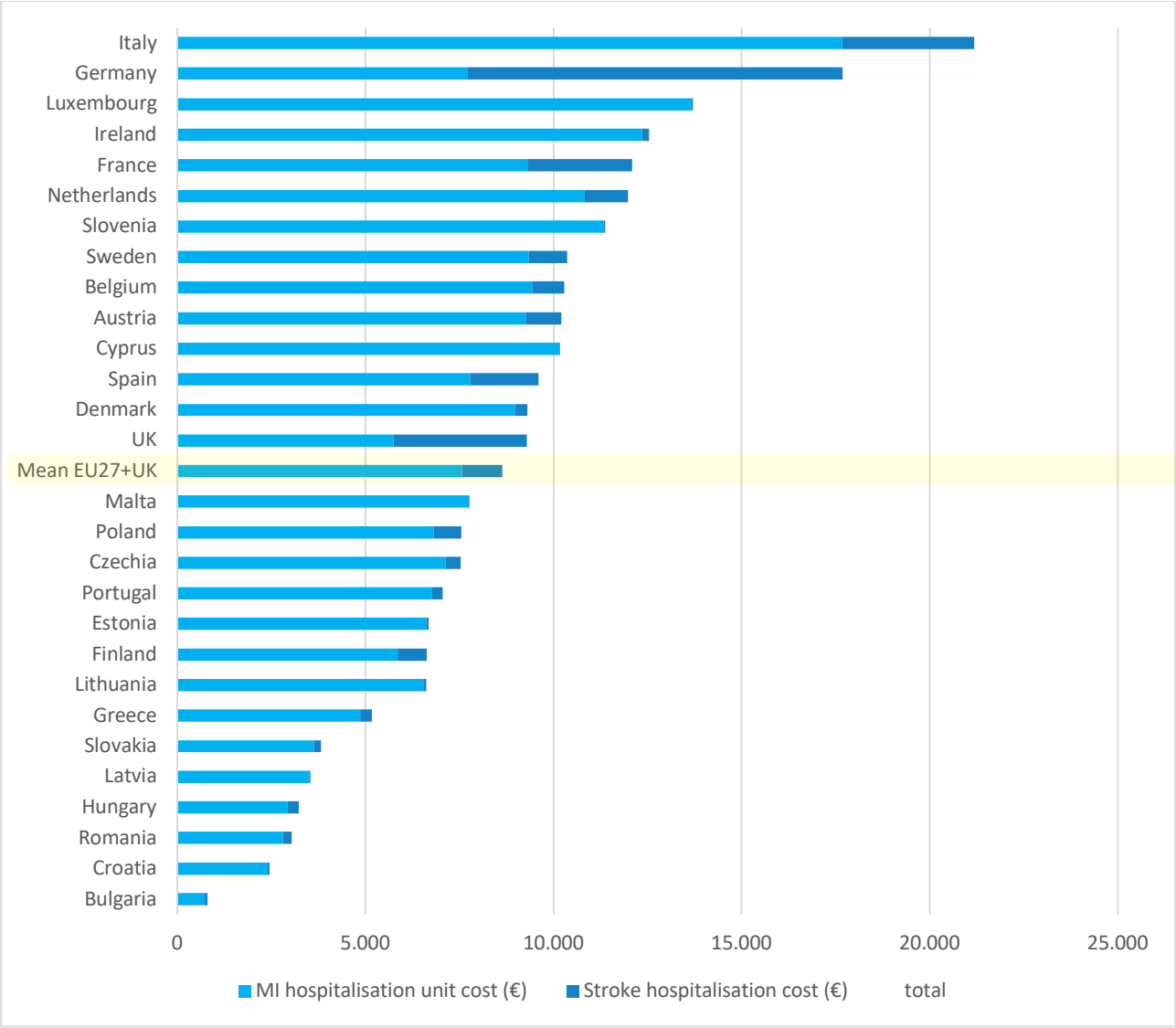

Figure 8.2.2: Per-case MI and stroke hospitalisation costs relative to EU27+UK mean.

The result is that their aggregate MI hospitalisation expenditure, while substantial in absolute terms, understates the true resource intensity of their cardiovascular burden relative to what the same event volumes would cost in a Lower tier health system.

Stroke hospitalisation generates the most extreme cost differential of any cardiovascular event type in our analysis. Indeed, hospital care costs for acute stroke range from €13 in Cyprus and Malta to €9,954 in

Germany and €3,542 in the UK, with the Very High tier recording a mean of approximately €167 per acute stroke admission against a Lower tier mean of approximately €1,177, a sevenfold gap that substantially exceeds the mortality and hospitalisation rate differentials between the same country groups.

The percentage of total stroke costs attributable to hospital care also varies markedly, from 16.1% in Malta and 22.3% in Latvia to 70.1% in Sweden and 69.5% in Finland, reflecting fundamental differences in stroke care pathway design. In higher-resource systems, acute inpatient care is the primary cost centre because comprehensive stroke unit infrastructure, thrombolysis, and mechanical thrombectomy are standard of care. In lower-resource systems the acute hospitalisation cost is lower but the downstream burden, uncompensated disability, informal caregiving, and lost productivity, is proportionally larger and less visible within the direct cost accounting.

France (€2,773) and Italy (€3,507) sit at the upper end of the Southern and Western European distribution, consistent with their investment in comprehensive stroke care pathways, while Croatia (€52), Latvia (€32), and Bulgaria (€78) record acute stroke costs that reflect both lower tariff structures and more limited acute stroke infrastructure. Given that stroke generates the highest per-case long-term care and disability costs of any cardiovascular event type,[4] and that the EU27+UK mean stroke incidence of 0.05% among males and 0.04% among females documented in section 2.1.2 translates to approximately 200,000 new stroke events annually, even modest reductions in stroke incidence attributable to risk factor modification generate disproportionately large direct cost savings relative to the number of events prevented.

Coronary revascularisation procedures

Coronary revascularisation procedures, percutaneous coronary intervention and coronary artery bypass grafting, represent a concentrated, high-unit-cost component of direct cardiovascular expenditure. Across the EU27+UK, an estimated 1,303,400 PCI and 159,100 CABG procedures are performed annually, a combined total of approximately 1,462,500 revascularisation procedures. Germany alone accounts for 353,100 of these, followed by France (224,400), Italy (166,900), and the UK (124,200), with the four largest economies together representing approximately 59% of total EU27+UK revascularisation volume. Among the Very High-risk tier countries, Romania (36,400), Czechia (32,100), Poland (110,200, classified High tier), and Hungary (26,700) record the highest absolute procedure volumes, reflecting both their elevated IHD incidence and the expansion of interventional cardiology capacity in those health systems over the past decade.

The cost per procedure amplifies the geographic inequality already documented for hospitalisation. Average PCI costs range from €2,100 in Bulgaria to €7,350 in Luxembourg, while CABG costs range from €4,200 in Bulgaria to €14,700 in Luxembourg, in both cases a 3.5-fold differential between the lowest and highest cost environments.

The Very High tier means PCI cost of approximately €2,764 compares with a Lower tier mean of approximately €6,418, meaning that the same revascularisation procedure generates more than twice the direct cost in a Lower tier health system than in a Very High tier system.

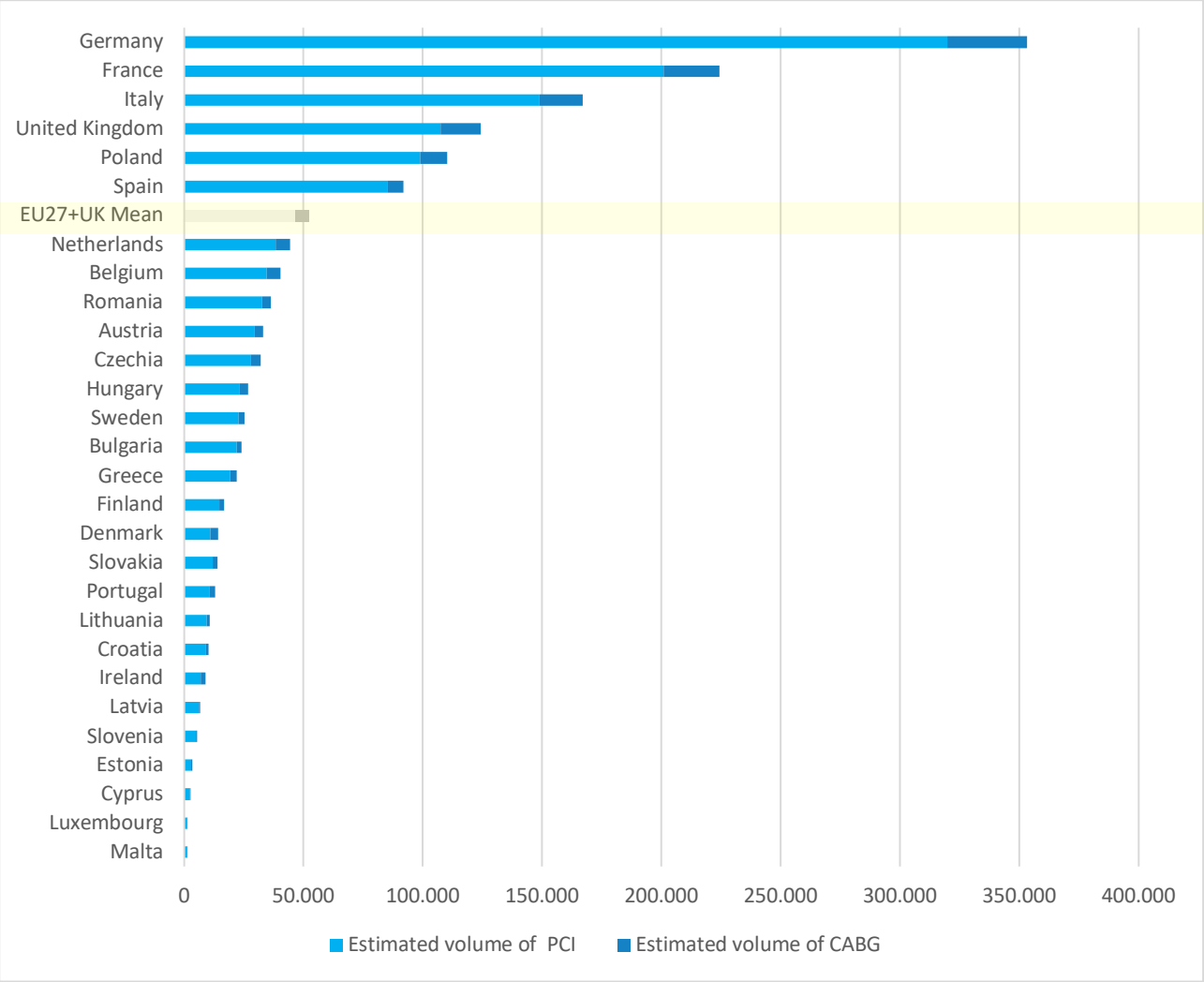

Figure 8.2.3: Total revascularisation volume by country, split Percutaneous Coronary Intervention (PCI) vs Coronary Artery Bypass Grafting (CABG)

Applied to the estimated Very High tier revascularisation volume of approximately 147,500 procedures annually, Bulgaria, Croatia, Czechia, Hungary, Latvia, Lithuania, and Romania combined, the aggregate direct revascularisation cost for the Very High tier stands at approximately €530 million, a figure that would exceed €945 million if the same procedures were performed at Lower tier cost levels. This cost compression in the highest-burden countries is not an indicator of efficiency: it reflects the structural underinvestment in procedural infrastructure and the lower DRG tariff environments documented in section 2.1.8, where Very High tier health expenditure per capita averaging €2,831 is less than half the Lower tier mean of €6,486.

Cardiac rehabilitation

Cardiac rehabilitation represents both a direct cost line and the clearest example of systematic underinvestment generating larger downstream costs across the EU27+UK.

Participation rates vary from 12.5% in Bulgaria, Cyprus, Estonia, Hungary, Portugal, and Spain to 87.5% in Lithuania and Luxembourg, with the EU27+UK mean standing at approximately 37.5% of eligible post-event patients. The Very High tier mean participation rate of approximately 33% is below even this modest average, and the clinical consequences are direct: meta-analytic evidence confirms that structured cardiac rehabilitation reduces cardiovascular mortality by 20–26% and rehospitalisation rates by 18–25% in secondary prevention populations, meaning that each percentage point of additional participation translates into measurable reductions in the repeat hospitalisation costs that constitute the largest ongoing component of secondary prevention expenditure.

The cost per cardiac rehabilitation programme ranges from €1,200 in Bulgaria to €4,200 in Luxembourg, with a EU27+UK mean of approximately €2,700. The inversion that emerges from combining participation rates with per-programme costs is analytically significant for the cost-savings model: Bulgaria, Hungary, and Croatia, countries with 12.5% participation rates and among the lowest per-patient rehabilitation costs in the dataset (€1,200, €1,600, and €1,500 respectively), could deliver the largest absolute reductions in rehospitalisation costs at the lowest marginal rehabilitation cost per patient reached. A ten percentage point increase in cardiac rehabilitation participation in Bulgaria alone, applied to its estimated secondary prevention population of approximately 85,000 patients, would generate approximately 8,500 additional programme completions at a total cost of approximately €10.2 million, against an estimated rehospitalisation cost avoidance of substantially greater magnitude given that a single repeat MI admission in Bulgaria costs €726 and that rehospitalisation rates in unrehabilitated patients average 18–25% higher than in rehabilitated populations. Lithuania presents the most anomalous profile in the dataset: a participation rate of 87.5%, the highest alongside Luxembourg, combined with a per-patient cost of only €1,600, substantially below the EU average, suggesting that high-volume, lower-cost rehabilitation delivery is achievable within a Very High tier health system when the institutional commitment to post-event care infrastructure is present.

Taken together, the five components of direct healthcare cost, acute MI hospitalisation, stroke hospitalisation, revascularisation procedures, pharmaceutical management, and cardiac rehabilitation, reveal a geography in which the countries carrying the greatest absolute cardiovascular event burden are systematically under-resourced to manage it.

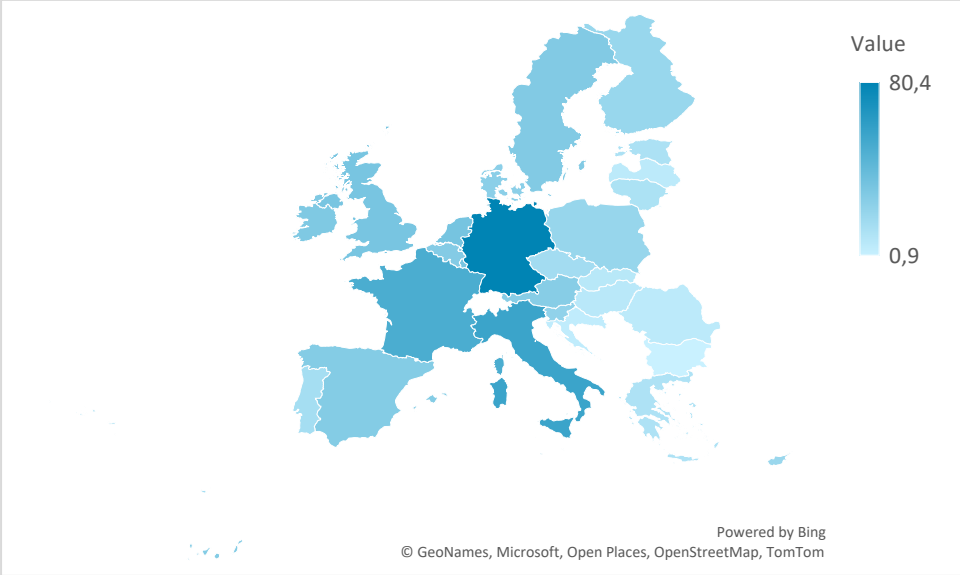

Figure 8.2.5: Direct CVD Care Expenditure Intensity, EU27+UK[70]

Comparing direct CVD expenditure across EU27+UK countries is complicated by the fact that the available data combine unit costs, procedure volumes, and aggregate spending figures that are not directly addable. To produce a coherent cross-country ranking, we constructed a composite index from four components, procedure cost per capita (PCI and CABG volume × unit cost, 35%), MI hospitalisation unit cost (30%), stroke hospital care cost (25%), and cardiac rehabilitation cost per patient (10%). Each component was normalised to a 0–100 scale before weighting to ensure comparability across different units of measurement. This index measures direct CVD care expenditure intensity, not efficiency or outcomes. Countries ranking lowest, Bulgaria, Croatia, Latvia, Romania, Hungary, spend least on direct CVD care because their unit costs are lower and procedure volumes are constrained by system capacity. This reflects underinvestment and undertreatment, not effective prevention. The highest-ranking countries, France, Italy and Germany record elevated scores primarily through procedure volume rather than unit cost alone.

The cost compression in Very High tier countries is not a reflection of efficiency but of constraint: lower per-case costs combined with higher event volumes produce aggregate direct cost burdens that are substantial in absolute terms but that absorb a disproportionate share of health system capacity relative to the financial resources available. The aggregate direct healthcare cost of CVD across the EU27+UK, estimated at approximately €155 billion annually, therefore understates the true resource intensity of the burden in the countries where prevention would generate the greatest return, and overstates the fiscal headroom available in those systems for additional pharmacological management. It is precisely in this gap, between the cost of reactive treatment and the cost of evidence-based preventive intervention, that the supplementation cost-savings model presented in section 5 is positioned.

[70] Composite index based on four components weighted by analytical role. All components normalised 0–100 before weighting. See methodology in appendix.

8.2.3 Indirect Costs and Productivity Losses

The aggregate statistics presented in the preceding sections describe a Union-wide burden that is real and severe. They do not, however, describe a burden that is evenly distributed. Cardiovascular disease in the EU is not a common condition with common consequences: it is a condition whose incidence, treatment, and cost consequences are systematically concentrated among the countries least equipped to bear them, in the populations least able to access the care that would reduce it, and in the socioeconomic groups for whom the financial barriers to prevention and treatment are highest.

Figure 8.2.6 shows the structural injustice of the access barrier: countries in the upper left quadrant (low spending, high OOP) are simultaneously those with the highest CVD burden bubbles. Bulgaria, Latvia, Greece, and Lithuania cluster in the danger zone. France, Luxembourg, and Croatia sit in the lower left (low OOP, low-moderate spending). Germany, Austria, and Ireland are high spending, low OOP.

No country is high spending and high OOP, confirming that OOP is not driven by wealth but by system design failure. This is the most analytically powerful single visual in the section.

Understanding this distribution is not a supplementary concern to the economic burden analysis, it is its analytical core. The case for preventive nutritional intervention is strongest precisely where the formal healthcare system is least able to provide the alternative.

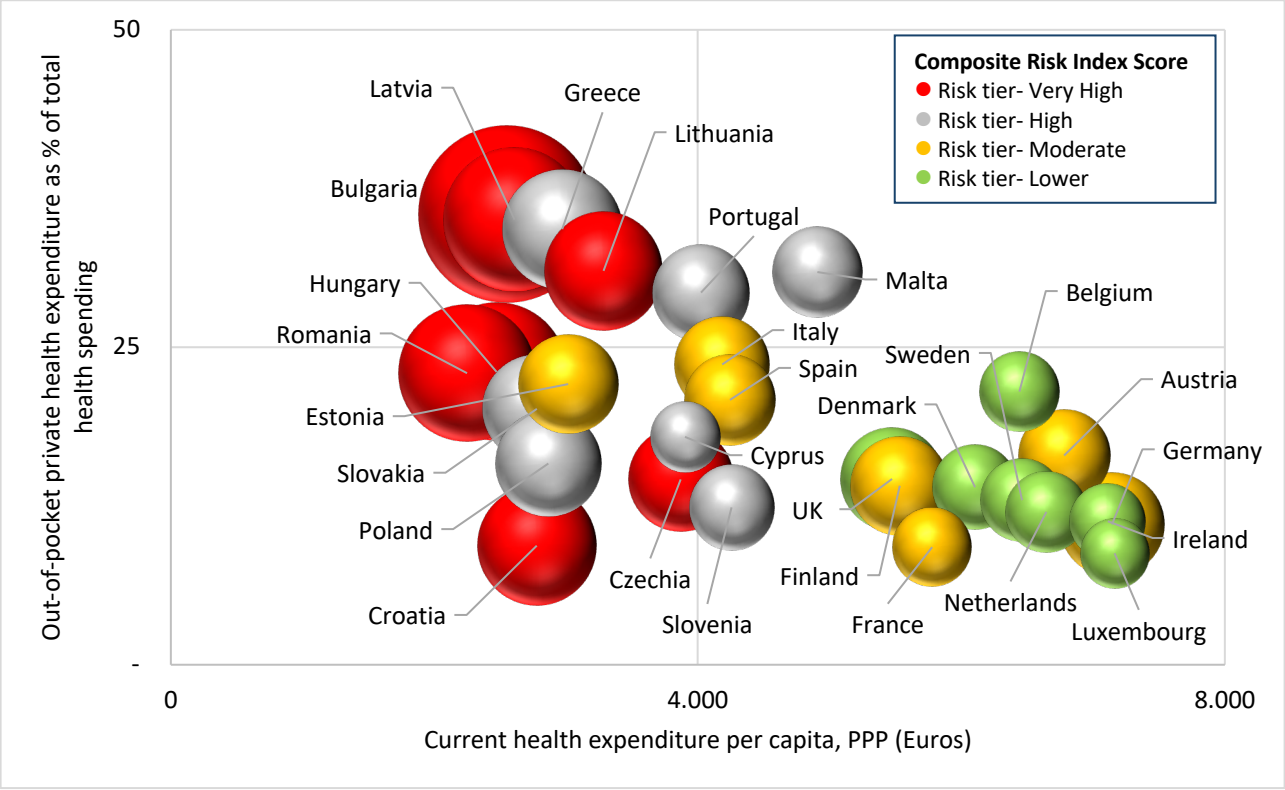

Figure 8.2.6: Health expenditure per capita (x-axis) vs OOP share (y-axis), bubble sized by working-age CVD death rate, country labelled.

The health system resource gap: nearly twice the spending for half the disease

Western EU Member States spend on average €6,489 per capita on health annually, nearly twice the €3,460 per capita spent by eastern EU Member States, countries that simultaneously carry CVD working-age death rates averaging 19.2% compared to 13.6% in western comparators (World Bank/Eurostat, 2023; IHME, 2023). The range is stark in individual country terms. Germany and Luxembourg spend €8,306 and €8,329 per capita respectively, 3.2 and 2.8 times the €2,614 spent by Romania and €2,970 spent by Bulgaria. These are not marginal differences in healthcare generosity, they are structural differentials that determine what interventions are available, how quickly acute cardiovascular events are treated, whether preventive services reach high-risk populations, and how thoroughly risk factors such as familial hypercholesterolaemia are detected and managed before they generate events.

The per capita health expenditure differential translates into a treatment access gap that is measurable across multiple dimensions. The most precisely quantifiable of these is familial hypercholesterolaemia (FH) diagnosis, a condition affecting approximately 0.3 to 0.4% of the EU population and representing one of the highest individual CVD risk states amenable to early lipid-lowering intervention.

FH diagnosis rates vary substantially across EU27+UK, from 71% of estimated FH cases identified in the Netherlands, where national cascade screening and genetic testing programmes have been in operation since 1994, to below 5% in Bulgaria, Romania, Latvia, Hungary, and Portugal, where fragmented care pathways, limited genetic testing capacity, and low clinical awareness combine to leave the overwhelming majority of FH patients undiagnosed and therefore untreated (Nordestgaard et al., 2013; Vallejo-Vaz et al., 2018; Umans-Eckenhausen et al., 2001). Among countries with active national programmes the detection gap spans more than a factor of twenty. Across the full EU27+UK dataset the range is wider still, with France and Italy recording diagnosis rates of approximately 1% as of the most recent systematically comparable estimates, though both countries have expanded their lipid clinic and regional screening infrastructure since those estimates were produced and current rates are likely higher (Nordestgaard et al., 2013).

Countries with active national cascade screening programmes, the Netherlands (71%), Sweden (25%), Luxembourg (25%), Denmark, and France, detect FH at rates that reflect decades of coordinated investment in lipid clinic networks and genetic testing infrastructure. Countries with partial programmes, the UK (12%), Finland, Austria, and Czechia, reach between 10% and 20% of their estimated FH populations. The remaining fourteen EU27+UK countries, concentrated in central and eastern Europe, remain below 10%, with Bulgaria (3.5%), Romania (4.0%), Belgium (4.0%), Slovakia (4.0%), and Spain (6.0%) among those with the lowest detection rates relative to estimated FH burden (Nordestgaard et al., 2013; Vallejo-Vaz et al., 2018). In practical terms this means that in Bulgaria and Romania, approximately 96% of people carrying a genetic mutation that doubles or triples their lifetime risk of premature myocardial infarction remain unaware of their condition.

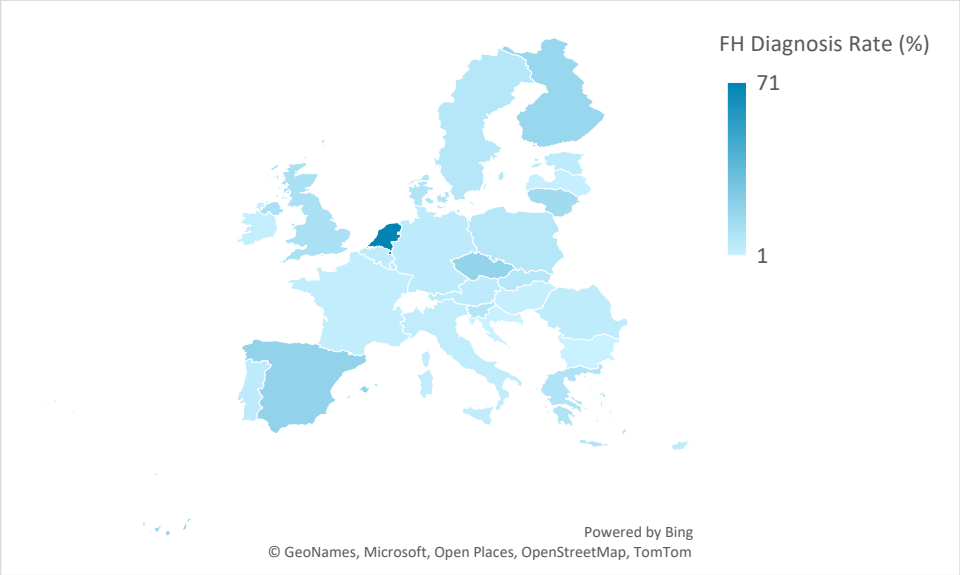

Figure 8.2.7 Familial hypercholesterolaemia estimated diagnosis rates by country, EU27+UK.

Note: FH prevalence based on population frequency of 1/500 (0.2%) for most countries; Nordestgaard 2013 uses 1/500 as denominator; some FHSC estimates use 1/250–1/500 range. Sources: Nordestgaard et al. (2013) European Heart Journal Figure 1 for eight countries; Vallejo-Vaz et al. (2018) FHSC registry for remaining twenty countries. Nordestgaard 2013 values represent estimates as of approximately 2012.

† Nordestgaard 2013 figures represent estimates as of approximately 2012. Denmark, France, Belgium, and Italy have each expanded FH screening infrastructure since that date; current diagnosis rates in these countries are likely higher than reported here. Range: 1.0% (France, Italy) to 71.0% (Netherlands). Unweighted EU27+UK mean: 11.2%.

The FH detection gap is the most precisely quantifiable expression of a broader prevention failure that operates across all CVD risk factor management. The same structural barriers, low health expenditure, high OOP costs, income inequality that limits access to preventive care for lower-income populations, which suppress FH diagnosis also suppress hypertension treatment, statin initiation rates, and the adoption of nutritional interventions for cholesterol management. In the countries where the CVD burden is highest and the economic consequences most severe, the formal healthcare system's capacity to deliver the preventive care that would reduce that burden is most constrained. This convergence of high burden and low prevention capacity is the structural argument for food supplement-based nutritional interventions as a policy lever: accessible without prescription, affordable at individual level, and operable independently of the formal care pathway through which the highest-risk populations are least likely to pass.

Out-of-pocket payments: the highest burden falls on those least able to pay

Out-of-pocket expenditure, the proportion of healthcare costs falling directly on individuals and families rather than absorbed by public insurance or mandatory health schemes, varies from 9% of total health spending in France, Croatia, and Luxembourg to 36% in Bulgaria and 35% in Latvia (World Bank/Eurostat,

2023). This range represents the difference between a healthcare system in which financial barriers to accessing CVD prevention and treatment are largely absent, and one in which those barriers are severe, regressive, and structurally concentrated among the populations carrying the highest disease burden.

The most analytically important finding from the OOP data is not the percentage share itself but the absolute cost it generates at individual level. Because eastern EU countries combine high OOP shares with low total health expenditure per capita, the absolute amount that patients must pay out of pocket is frequently higher in nominal terms than in wealthier western EU countries with lower OOP shares. Bulgaria, where OOP represents 36% of a €2,970 per capita health budget, generates an absolute out-of-pocket healthcare cost of €1,069 per person annually. Lithuania reaches €1,184 and Greece €1,174. By contrast, France, where OOP represents only 9% of a €6,719 per capita budget, generates an absolute OOP cost of just €605. A Bulgarian patient therefore pays more in absolute terms for their share of healthcare than a French patient does, despite having access to a system spending less than half as much per capita in total (World Bank/Eurostat, 2023).

This inversion has direct consequences for cardiovascular prevention. Out-of-pocket costs operate as a rationing mechanism that is not clinically neutral, they systematically suppress utilisation among lower-income households, older adults on fixed incomes, and populations in rural or underserved areas, which is precisely the demographic profile of the highest CVD risk groups in eastern and south-eastern EU

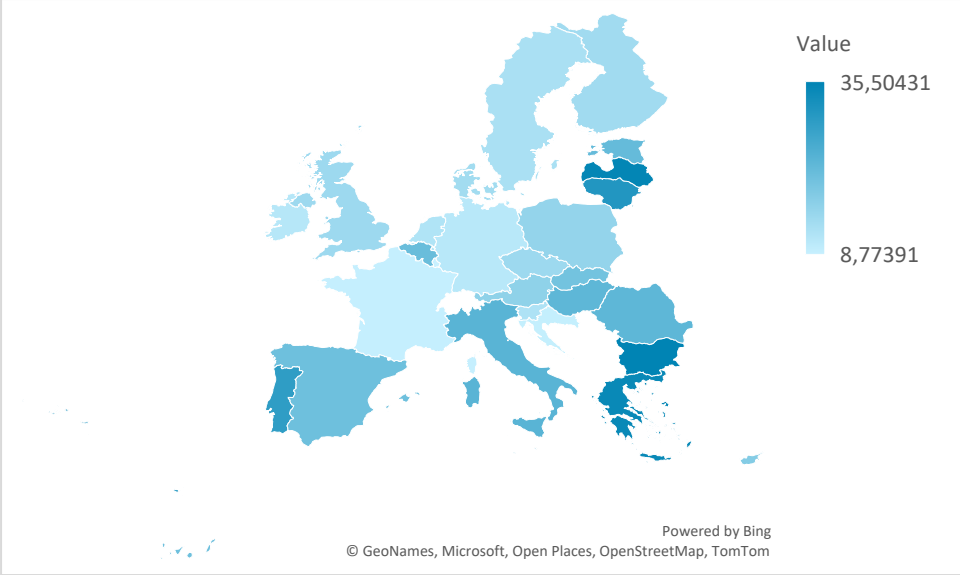

Figure 8.2.8: Out-of-pocket private health expenditure as % of total health spending (2023)

The patients in Bulgaria, Latvia, Lithuania, and Romania who carry the highest premature CVD death rates and the widest FH detection gaps are simultaneously the patients facing the highest absolute financial barrier to the preventive cardiovascular consultations, lipid tests, and pharmacological or nutritional interventions that could reduce their risk. The OOP payment structure does not simply reflect the disease burden; it actively amplifies it by suppressing the prevention and early detection activity that would reduce future acute events and hospitalisations.

The compound effect of income inequality layered onto OOP burden deepens this dynamic further. Bulgaria records the highest Gini coefficient in the dataset at 39.5 alongside its 36% OOP share, meaning that within a country already facing the highest absolute OOP costs, the distribution of those costs falls most heavily on the lowest-income households. Latvia (Gini 34.0, OOP 35%), Lithuania (Gini 36.0, OOP 31%), and Greece (Gini 33.4, OOP 34%) each combine high income inequality with high absolute OOP burden, producing a structural environment in which CVD prevention is effectively priced out of reach for the socioeconomic groups most exposed to cardiovascular risk. In a highly unequal society with high OOP costs, the wealthiest quintile absorbs the financial barrier to cardiovascular care without behavioural change; the poorest quintile cannot access even the most basic preventive services, not because of clinical ineligibility but because of cost. This is the precise mechanism through which income inequality translates into cardiovascular mortality inequality at population level.

Croatia is the notable exception within the eastern EU cluster. Despite low health expenditure per capita (€3,229), Croatia records an OOP share of only 9%, the joint lowest in the EU27+UK alongside France and Luxembourg, resulting in an absolute OOP burden of just €291 per capita, the lowest in the dataset. This reflects Croatia's social health insurance architecture, which maintains broad population coverage and low cost-sharing requirements despite constrained total healthcare resources. Croatia demonstrates that low OOP burden is a health system design choice rather than a simple function of national income, and that the high OOP shares seen elsewhere in eastern Europe are not structurally inevitable but represent policy decisions with direct cardiovascular health consequences.

The geographic coherence of the inequality

The four indicators examined in this section, health expenditure per capita, OOP share, income inequality, and FH diagnosis rate, converge on the same geographic cluster with a consistency that is not coincidental. Bulgaria, Latvia, Romania, Hungary, and Lithuania appear in the adverse quartile on every dimension: low health expenditure, high OOP share, high income inequality relative to health expenditure levels, and extremely low FH detection. These are the same five countries that record the highest CVD working-age death rates, the highest premature mortality productivity losses relative to national wage levels, and the highest informal care burdens as a share of total CVD cost documented throughout this chapter. The inequality in cardiovascular burden across the EU is not a random distribution, it is a structured, geographically coherent inequality with identifiable determinants that are themselves amenable to policy intervention. The cost-savings model in the following chapter weights country-level projections against this inequality structure, reflecting the differential economic return to preventive supplementation across the EU's risk and resource gradient.

8.2.4 The Unequal Distribution of Burden Across EU Member States

The economic cost of cardiovascular disease falls disproportionately on the Member States least equipped to bear it. Countries recording the highest CVD mortality rates, Bulgaria, Romania, Latvia, Lithuania, Hungary, consistently record the lowest direct healthcare expenditure per event, the highest out-of-pocket payment

burdens, and the lowest rates of preventive intervention such as familial hypercholesterolaemia diagnosis and lipid-lowering treatment coverage. This is not a coincidence of geography. It reflects a structural misalignment between disease burden and health system capacity that compounds over time: undertreated risk factors generate more events, more events generate more costs that systems cannot absorb, and more costs fall on individuals and households already carrying the greatest disease burden. At the other end of the distribution, Western European countries including Germany, France, Italy, and Ireland carry high direct CVD costs driven by high procedure volumes, high unit costs, and intensive rehabilitation programmes, but also achieve materially better cardiovascular outcomes in terms of age-standardised mortality and post-event survival. Higher expenditure in these countries reflects both greater disease management intensity and greater system capacity to intervene early, not simply higher prices for the same outcomes.

The practical implication for this report is that the economic return to preventive supplementation is not uniform across the EU27+UK. In high-burden Eastern European countries, the primary value is in preventing acute events in populations with high incidence and limited treatment access. In higher-expenditure Western European countries, the primary value is in reducing costly hospitalisations and revascularisation procedures in a large and growing prevalent CVD population.

8.2.5 The Growing Burden: Demographic and Epidemiological Projections

Population ageing is the single most important structural driver of future CVD burden across the EU27+UK, and it is already embedded in the demographic data through 2035. The 55 and over population, the age group in which absolute cardiovascular event risk is highest and in which the supplementation interventions modelled in this report are most clinically indicated, is growing in every Member State. In Germany, Italy, France, Spain, and the UK, this cohort will exceed 20 million by 2035, sustaining high absolute CVD event volumes even where age-standardised mortality rates continue to decline. In Eastern European countries where total populations are contracting, Romania, Bulgaria, Latvia, Lithuania, the apparent stabilisation or modest decline in absolute CVD death counts projected to 2035 reflects demographic shrinkage rather than improved prevention and should not be interpreted as evidence of a diminishing prevention opportunity.

Layered onto this demographic trend is a deteriorating metabolic risk environment that will increasingly offset the gains from improved acute care. Obesity among adults aged 55 and over already exceeds 40% in Hungary, Malta, and Portugal. Physical inactivity affects more than 70% of adults in Croatia. Sodium intake remains substantially above recommended levels across Central and Eastern Europe. These upstream exposures will sustain and, in some geographies, increase CVD incidence over the forecast period, expanding the eligible population for preventive supplementation even as acute care capabilities improve.

The economic model projects event counts and cost savings across 2025 and 2035 using the country-level population and demographic data established in this chapter, capturing both the expanding size of the eligible population and the shifting geographic distribution of burden over the decade. The cost-savings analysis translates this prevention opportunity into projected economic returns across the EU27+UK, quantifying the net benefit of Omega-3 EPA+DHA, Phytosterol, and Beta-Glucan supplementation across

the modelled coverage scenarios and providing an evidence base for assessing their potential contribution to cardiovascular prevention.

8.2.6 CVD Burden forecast to 2035

Total CVD costs across the EU27 and UK are estimated at €310.0 billion in 2021, the reference year established by Luengo-Fernández et al. (2023) and corroborated by the OECD (2025). This figure represents the most comprehensive and methodologically rigorous cross-national estimate of CVD economic burden available, encompassing health and social care, informal care, and productivity losses across all 28 countries.

Between 2021 and 2023, total costs declined to an estimated €299.8 billion, a fall of approximately 3.3% over two years. This contraction does not reflect a genuine reduction in CVD disease burden, which remained substantial throughout the period. Rather, it reflects two converging macroeconomic effects. First, real GDP contracted or stagnated in several major economies, most notably Germany (−0.9% in 2023), the Netherlands, Denmark, and the Baltic states, compressing the economic base against which CVD costs are estimated. Second, health expenditure as a share of GDP fell sharply across most EU countries as pandemic-era emergency spending unwound from its 2021 peak, Germany's CHE/GDP ratio declined by nearly one percentage point between 2021 and 2023, France's by 0.7 percentage points. Since the 2021 Luengo-Fernández base was measured at a moment of transitorily elevated healthcare expenditure intensity, the subsequent normalisation is best understood as mean reversion rather than structural improvement.

From 2024, costs begin to recover, reaching an estimated €302.7 billion in 2024 and €307.3 billion in 2025, as GDP growth resumes across most EU economies and health expenditure ratios stabilise. This upward inflection marks the beginning of the structural growth trajectory projected through 2035, driven by population ageing and rising healthcare utilisation.

8.3 Target Population Definition

8.3.1 Purpose and scope

A precisely defined target population is essential for a credible cost-savings model. The efficacy parameters derived from the clinical evidence reviewed in Section 4 apply specifically to adults with elevated cholesterol rather than to the general adult population. Applying these parameters to an overly broad population would overstate the plausible benefit and undermine the analytical credibility of the model. Equally, defining the population too narrowly would understate the scale of the prevention opportunity and produce projections that do not reflect the real-world distribution of cardiovascular risk across the EU27+UK.

The target population for the Phytosterols and Beta-Glucan cost-savings models is adults aged 55 and above residing in the EU27 and UK with elevated total cholesterol, including those with familial hypercholesterolaemia. This definition reflects the lipid-lowering positioning of both interventions and provides a clinically relevant population in which reductions in LDL-cholesterol can be translated into potential reductions in cardiovascular event risk. The eligible population is not restricted according to

statin-use status; individuals receiving statin therapy therefore remain within the addressable population for the purposes of the model.

The operational eligible population is derived from the full high-total-cholesterol population aged 55 and above. Country-level high-total-cholesterol prevalence derived from IHME GBD 2023 is applied to Eurostat population projections to estimate the eligible population across the EU27+UK. No statin-naïve filter is applied to the Phytosterol or Beta-Glucan populations. This produces an eligible population of approximately 83.7 million adults in 2025, which is the denominator applied to the Phytosterol and Beta-Glucan avoidable-event and cost calculations.

8.3.2 Age boundary rationale

The clinical trial evidence underpinning the efficacy parameters applied in this model was generated predominantly in adults aged 40 and above. The primary meta-analytic framework (Gorini et al. 2024; Llanaj et al. 2022; Yan et al. 2024) enrolled adults with mean ages of approximately 55–65 years, broadly consistent with the 55-plus eligible population. The Gorini et al. (2024) meta-analysis of 14 RCTs included populations with mean ages predominantly in the 50–65 range. These age distributions are also consistent with the broader cardiovascular risk-reduction evidence base, including the CTT meta-analysis covering 174,000 participants, which found that relative cardiovascular risk reduction associated with LDL-C lowering remained evident across age subgroups, including adults aged 65 and above.

For the purposes of this model, the population aged 55 and above is applied as the operational eligible age band for three reinforcing methodological reasons. First, the MACE endpoint used throughout this model, defined as the aggregate incidence burden of cardiovascular disease in the population aged 55 and above derived from IHME GBD 2023 data applied to Eurostat population projections, is itself anchored to the 55-plus age group. Maintaining consistency between the MACE burden denominator and the eligible population denominator is essential for the internal validity of the ARR and NNT calculations. Second, the burden of ischaemic heart disease and stroke is overwhelmingly concentrated in adults aged 55 and above across the EU27+UK, accounting for approximately 90% of all IHD and stroke incident cases. Third, the RRR parameters applied in this model are derived from trials in which the mean participant age was typically in the 60–65 range, making the 55-plus population a closer demographic match to the actual trial population than any broader age band. To the extent that any bias is introduced by this restriction, it operates in the conservative direction: absolute risk reduction per person is larger in older populations with higher baseline event rates.

8.3.3 Biological rationale for population targeting

The primary mechanisms through which Phytosterols and Beta-Glucan reduce cardiovascular risk are LDL-C lowering via intestinal cholesterol absorption reduction and bile acid sequestration respectively, as documented in Section 4.4.1. This mechanism is most clinically operative in populations whose baseline LDL-C sits above the threshold at which LDL-C reduction generates meaningful risk reduction, broadly,

adults with LDL-C at or above 3.0 mmol/L, which is the lower bound of the mild-to-moderate hypercholesterolaemia range targeted in the ESC/EAS 2019 clinical positioning.

The eligible population denominator used in this model, adults aged 55 and above with elevated total cholesterol including FH, serves as a practical operational proxy for this clinical criterion. Total cholesterol elevation is a validated upstream marker for LDL-C elevation, and the two measures are highly correlated at population level. The IHME GBD 2023 high total cholesterol prevalence data, defined as total cholesterol at or above 5.0 mmol/L, broadly captures the population in which LDL-C ≥3.0 mmol/L is prevalent, though the total cholesterol criterion is a wider net than the LDL-C threshold. This is a deliberate conservative choice: using the broader total cholesterol denominator ensures the eligible population is not artificially narrowed by the lack of a harmonised country-level LDL-C prevalence dataset across all 28 EU27+UK geographies.

The FH subpopulation is included in the eligible population on the basis that their severely elevated LDL-C profile places them in the highest-priority clinical group for LDL-C lowering interventions of any kind and that their exclusion would represent an analytically unjustified restriction of the eligible denominator. The FH prevalence estimation methodology is documented in full in section 8.9.

The three interventions are modelled at their base-case doses (Section 7.1.2). The Gorini et al. (2024) meta-analysis documents a mean LDL-C reduction of approximately 0.93 mmol/L and the Gould et al. (2007) / Ference et al. (2012, 2017) risk translation framework generates a projected MACE RRR of 20%. As documented in the regulatory disclaimer in Section 4, this dose exceeds the current EU regulatory limit of 3 mg per daily dose under Regulation (EU) 2022/860 and the proposed full prohibition under WTO notification G/SPS/N/EU/923. The model is presented as a theoretical economic reference scenario at the clinically effective dose.

8.3.4 Population sizing, baseline 2025

The baseline eligible population is derived from two primary data sources. Eurostat demographic projections provide the total population aged 55 and above for each of the 28 EU27+UK geographies for each year from 2023 to 2035. IHME Global Burden of Disease 2023 data provide the country-level prevalence of high total cholesterol, expressed as a proportion of the total population, from which the 55-plus share is derived by applying the age-band proportioning methodology described below.

Across the EU27+UK, the 55-plus population in 2025 is estimated at approximately 174 million. Applying IHME 2023 high total cholesterol prevalence rates to the 2025 Eurostat population, the full high total cholesterol 55-plus population is approximately 83.7 million adults, approximately 49% of the 55-plus population. The resulting eligible population for the Phytosterol and Beta-Glucan models is approximately 83.7 million adults in 2025. No statin-naïve filter is applied, and this full high-total-cholesterol population aged 55 and above is the denominator used for the Phytosterol and Beta-Glucan avoidable-event and cost calculations in the base-case model.

8.3.5 Adoption scenarios

The model applies a 100% population coverage scenario for each intervention, comparing supplementation of the full eligible population with a counterfactual baseline of zero supplementation. The base-case interventions are Omega-3 EPA+DHA at 1,000 mg/day, Phytosterols at 1.5 g/day, and Beta-Glucan at 3.0 g/day, corresponding to MACE relative risk reductions (RRRs) of 5.0%, 7.0%, and 6.4%, respectively. This 100% coverage design produces a theoretical ceiling estimate of the maximum addressable economic value under ideal conditions and is not a forecast of expected real-world uptake.

The ceiling estimate methodology serves two analytically distinct purposes. First, it quantifies the potential public health and economic opportunity if the eligible populations were fully covered at the modelled supplement doses and costs. Second, it ensures that results are comparable across all 28 EU27+UK geographies without introducing assumptions regarding differences in market penetration, consumer awareness, healthcare professional recommendation, or supplement access. The eligible population differs by intervention according to the risk factor targeted: Omega-3 is modelled in the population with elevated triglycerides, while Phytosterols and Beta-Glucan are modelled in the population aged 55 and above with elevated total cholesterol.

Policymakers and commercial stakeholders seeking projections calibrated to more realistic uptake levels can derive these by applying alternative population coverage assumptions to the model outputs. Because the model estimates the economic impact under full eligible-population coverage, lower uptake scenarios provide proportionately lower estimates of avoidable events, gross healthcare cost savings, supplement costs, and net economic benefit.

8.3.6 Forecast to 2035

The eligible population is projected forward to 2035 using country-level Eurostat population forecasts. Across the EU27+UK, the total population aged 55 and above is projected to grow from approximately 173 million in 2023 to approximately 175 million in 2035, with growth concentrated in Western and Southern European countries and contraction in several Eastern European Member States including Latvia (−10.9%), Lithuania (−8.3%), Bulgaria (−7.7%), and Romania (−6.1%), due to the combined effects of emigration, lower birth rates, and natural population decline.

Risk factor prevalence rates are held constant at their base-year values across the projection window. Changes in the eligible population over the 2023–2035 horizon are therefore driven by demographic change rather than by assumed changes in the prevalence of elevated cholesterol. For Phytosterols and Beta-Glucan, the eligible population comprises the full population aged 55 and above with elevated total cholesterol, with no adjustment for statin use. Changes in this population over the projection period therefore reflect the evolution of the underlying 55-plus population across the EU27+UK. Growth in gross societal cost savings over the projection window reflects the combined effect of demographic change and rising societal cost per incident CVD case.

8.4 Frost & Sullivan Composite Cardiovascular Risk Index Methodology

8.4.1 Step 1: Indicator selection

Seven modifiable risk indicators were selected for inclusion in the composite index on the basis of three criteria applied jointly.

- First, each indicator must have a direct and well-characterised causal pathway to cardiovascular event risk supported by meta-analytic evidence from randomised controlled trials or large-scale prospective cohort studies.
- Second, each must be measurable at country level across the full EU27+UK geography from a single consistent data source with comparable methodology across countries.
- Third, each must capture a dimension of cardiovascular risk not already fully represented by another indicator already included in the set, ensuring that the index measures the breadth of the upstream risk environment rather than over-weighting any single causal pathway through correlated proxies.

The seven selected indicators are mean non-HDL cholesterol among males (NCD-RisC, 2018), mean systolic blood pressure among males (WHO/OECD, 2015), tobacco use prevalence among adults aged 15 and over (WHO, 2025), estimated sodium intake among adults aged 25 and over (GBD, 2019), physical inactivity expressed as the proportion of adults aged 18 and over not achieving 300 minutes of moderate-intensity activity per week (WHO, 2017), obesity prevalence among adults aged over 55 expressed as the mean of male and female prevalence (NCD-RisC, 2022), and total per capita alcohol consumption among adults aged 15 and over (WHO, 2019).

The male sex was used for the lipid and blood pressure indicators because sex-disaggregated data are available and because male values record systematically higher cardiovascular risk burden across the study geography, ensuring the index captures the peak of the risk distribution rather than its mean.

The over-55 age group was selected for obesity because it corresponds most directly to the demographic in which absolute cardiovascular event risk is concentrated and is consistent with the age framework used to define the eligible populations and MACE burden within the cost-savings model.

The GBD 2023 risk factor attribution data confirms that high systolic blood pressure, LDL cholesterol, tobacco, BMI, and sodium, all represented in the index, account for the five largest modifiable cardiovascular risk factor attributions in the European context.

The index conservatively excludes fasting plasma glucose, chronic kidney disease, and exposure to lead whose inclusion would likely amplify rather than reduce the Very High tier risk differential. Data availability and methodological coherence constraints preclude their inclusion in the current analytical framework.

8.4.2 Step 2: Normalisation

Because the seven indicators are measured in different units, millimoles per litre, millimetres of mercury, percentages, grams per day, litres per capita, they cannot be combined arithmetically in their raw form.

Each indicator was therefore normalised to a dimensionless 0–1 scale using min-max normalisation, defined as follows.

For each indicator, the normalised score for country is equal to the raw value for country minus the minimum raw value observed across all 28 countries, divided by the difference between the maximum and minimum raw values observed across all 28 countries.

This transformation ensures that the country recording the least favourable value in the dataset receives a normalised score of 1, the country recording the most favourable value receives a score of 0, and all other countries fall proportionally between these extremes in a manner that preserves the relative magnitude of differences between countries. A country that is only marginally worse than the minimum therefore receives a score only marginally above zero, rather than being artificially inflated toward 1 as would occur with a rank-based normalisation.

Physical inactivity was derived prior to normalisation by subtracting the reported proportion of adults achieving 300 minutes or more of moderate-intensity activity per week from 100, so that higher values consistently denote higher risk across all seven indicators and the normalisation function applies uniformly without sign reversal.

The minimum and maximum values used as normalisation anchors were drawn entirely from the EU27+UK country set and are therefore relative to the study geography rather than to global benchmarks. This means that a normalised score of 1 identifies the highest-risk country within the EU27+UK for a given indicator, not the highest-risk country in the world. For a study whose analytical and commercial purpose is to stratify risk and cost savings within the EU27+UK geography, this internal normalisation is the appropriate approach.

8.4.3 Step 3: Weighting

The seven normalised indicators were combined into a weighted composite score using the following weights, assigned based on the strength of causal evidence linking each indicator to cardiovascular event risk and to the food supplement interventions whose cost savings are modelled in this study.

Non-HDL cholesterol was assigned a weight of 20%. It is the primary atherogenic marker, the 2019 ESC/EAS primary treatment target, and the direct biological endpoint of LDL-C-lowering food supplement interventions. The Cholesterol Treatment Trialists meta-analyses across 175, 000 participants establish a relative risk reduction of approximately 21% per mmol/L LDL-C reduction, the most precisely quantified dose-response relationship in the cost-savings model.

Systolic blood pressure was assigned a weight of 20%. It is the primary haemodynamic determinant of stroke risk and a major independent contributor to coronary event risk, and it is the direct target of the Omega-3 EPA+DHA blood pressure reduction pathway. The Zhang et al. 2022 dose-response meta-analysis documents substantially larger absolute blood pressure reductions in populations with baseline SBP above 130 mmHg, making this indicator critical for the geographic stratification of Omega-3 cost savings.

Tobacco use was assigned a weight of 15%. Tobacco is an independent cardiovascular risk factor that amplifies LDL oxidation, depresses HDL cholesterol, and accelerates endothelial damage through

mechanisms that interact multiplicatively with the lipid and blood pressure pathways already captured by the first two indicators. The 2025 WHO data used for this indicator capture all tobacco product use rather than cigarette smoking alone, providing a more complete picture of the compound tobacco burden.

Sodium intake was assigned a weight of 15%. Dietary sodium is the most directly causal upstream dietary driver of blood pressure elevation, with meta-analytic evidence establishing a 3–5 mmHg systolic blood pressure reduction per 1 g/day sodium reduction. Its inclusion alongside systolic blood pressure is justified because it captures the structural dietary exposure generating hypertension rather than the current blood pressure outcome and therefore incorporates the future trajectory of hypertensive burden in addition to its current level.

Physical inactivity, over-55 obesity, and alcohol consumption were each assigned a weight of 10%. Physical inactivity independently drives dyslipidaemia, hypertension, and insulin resistance through multiple biological pathways. Over-55 obesity operates through hepatic hypertriglyceridemia and sympathetic-mediated hypertension, mechanisms that compound the atherogenic lipid and blood pressure burdens captured by the lipid and SBP indicators but are only partially represented by those indicators. Alcohol consumption drives blood pressure elevation through a well-characterised dose-response relationship and promotes hypertriglyceridemia through hepatic VLDL synthesis, both directly relevant to the Omega-3 EPA+DHA intervention pathway.

These three indicators were weighted equally at 10% because their cardiovascular risk contributions, while independently validated, are mechanistically overlapping with the higher-weighted indicators and their causal pathways to cardiovascular events are less directly quantified in the dose-response evidence base underpinning the cost-savings model.

The composite score for each country was computed as the sum of the products of each normalised indicator value and its assigned weight, producing a composite score between 0 and 1 for each country. Countries with composite scores at or above 0.65 were classified as Very High risk, scores of 0.50 to 0.64 as High risk, scores of 0.35 to 0.49 as Moderate risk, and scores below 0.35 as Lower risk.

These thresholds were selected to produce analytically meaningful and demographically coherent groupings; the Very High tier captures the countries for which every preceding layer of analysis in this chapter has consistently identified the most severe compound risk environment and should be interpreted as ordinal designations rather than precise statistical quantiles.

Rank	Country	Non-HDL (mmol/L)	Raised BP (%)	Tobacco (%)	Sodium (g/day)	Inactivity (%)	Obesity >55 (%)	Alcohol (L/cap)	Score	Risk tier
1	Croatia	3.83	37.3	37.6	5.1	84.1	41.9	13.8	0.859	Very High
2	Hungary	3.68	31.5	31.5	5.7	70.5	46.2	17.2	0.781	Very High
3	Bulgaria	3.78	29.7	38.8	5.1	55.4	27.2	19.5	0.742	Very High
4	Czechia	3.74	26.3	29.4	5.1	61.4	41	21.1	0.711	Very High
5	Latvia	3.86	31.7	32.6	3	66	37.2	21.7	0.711	Very High
6	Lithuania	3.86	29.9	30.2	2.9	65	40.2	19.3	0.673	Very High
7	Romania	3.65	15.7	29.3	5.1	71.2	43.6	27.3	0.666	Very High
8	Slovakia	3.64	28.4	32.8	5	33.4	38.2	16.7	0.64	High
9	Poland	3.67	26.5	22.1	4.4	55.5	40.6	18.7	0.598	High
10	Slovenia	3.74	25.4	19.5	5.1	41.6	25	17.3	0.548	High
11	Malta	3.76	18.1	23.9	3.8	79.7	41.9	13	0.545	High
12	Portugal	3.53	26.6	25.8	3.5	72.2	36.9	16.9	0.545	High
13	Cyprus	3.62	18.9	35	3.4	65.4	34.4	12.7	0.513	High
14	Greece	3.6	19.6	30.6	3.3	63.8	43.8	11.3	0.5	High
15	France	3.75	16.5	34.6	3	61.6	13.3	18	0.473	Moderate
16	Austria	3.76	21.8	22.5	3.4	38.7	20.4	18.8	0.457	Moderate
17	Italy	3.65	20.4	22.1	3.8	61.3	28.2	12.7	0.451	Moderate
18	Germany	3.44	26.2	19.7	3.4	46.9	31	19.2	0.437	Moderate
19	Finland	3.58	27.3	20.7	3.3	41	27.1	14.4	0.433	Moderate
20	Estonia	3.66	23.3	26.4	2.3	16.8	33.4	18.4	0.421	Moderate
21	Spain	3.34	19.3	27.8	3.2	51.4	26.5	17.3	0.375	Moderate
22	Luxembourg	3.4	15.5	22.3	3.4	48.4	26.2	17.6	0.335	Lower
23	Belgium	3.13	17.4	26.3	3.3	67.2	26.4	16.2	0.313	Lower
24	UK	3.35	24	12.5	2.8	39.4	32	17	0.306	Lower
25	Sweden	3.5	18.2	20.5	3.2	36.1	18.9	14.4	0.303	Lower
26	Netherlands	3.35	16.1	19.9	3.2	34.9	22.8	14.5	0.254	Lower
27	Ireland	3.24	11.6	17.8	2.9	40.7	39	18.1	0.244	Lower
28	Denmark	3.34	18.9	14.4	3.2	33.7	16.4	14.6	0.219	Lower

Table 6.4.1: Composite score by country

8.5 Methodology for Estimating Costs of CVD

8.5.1 Base year (2021)

Country-level total CVD costs for the EU27 are sourced directly from Luengo-Fernández et al. (2023), Economic burden of cardiovascular diseases in the European Union: a population-based cost study, European Heart Journal 44(45):4752–4767.

This is the most comprehensive and methodologically rigorous pan-European CVD cost-of-illness study available, covering all 27 EU member states for the reference year 2021 using country-specific data on morbidity, mortality, and health, social and informal care resource use.

Costs were valued using country-specific unit costs drawn from national tariffs, reimbursement schedules, and published studies, and were estimated from a societal perspective encompassing three components: health and social care (H&SC), informal care, and productivity losses.

The UK figure is sourced from Wilkins et al. (2017), Cardiovascular disease statistics 2017, British Heart Foundation, adjusted to 2021 EUR using UK healthcare cost inflation indices and the 2021 average GBP/EUR exchange rate, consistent with the approach applied in the OECD (2025) State of Cardiovascular Health in the European Union report, which cites the same combined EU27+UK aggregate.

Country	H&SC (€M)	Informal care (€M)	Productivity (€M)	Total (€M)
Austria	5,142	2,246	1,078	8,466
Belgium	3,940	1,547	1,310	6,797
Bulgaria	839	493	651	1,983
Croatia	406	507	195	1,108
Cyprus	186	54	69	309
Czechia	2,487	1,813	929	5,228
Denmark	2,001	979	1,413	4,392
Estonia	250	188	129	568
Finland	2,479	937	970	4,386
France	24,290	7,157	6,697	38,144
Germany	44,865	25,352	13,184	83,400
Greece	2,237	1,003	1,075	4,315
Hungary	1,848	852	921	3,621
Ireland	2,041	546	855	3,442
Italy	23,747	13,734	4,497	41,978
Latvia	252	205	293	750
Lithuania	559	406	473	1,439
Luxembourg	267	75	70	413
Malta	95	37	51	183
Netherlands	8,670	2,100	2,289	13,059
Poland	6,127	4,466	2,586	13,179
Portugal	1,803	1,245	723	3,772
Romania	2,220	2,806	1,396	6,421
Slovakia	942	562	459	1,964
Slovenia	632	292	124	1,048
Spain	13,063	7,434	3,462	23,960
Sweden	3,998	1,608	1,606	7,211
UK	13,521	6,096	9,582	28,470
EU27	**5,755**	**2,913**	**1,759**	**10,427**
EU27+UK	**6,032**	**3,026**	**2,039**	**11,072**

Table 8.5.1 – Cost of CVD by country in 2021

8.5.2 Extrapolation framework (2022–2035)

In the absence of annual CVD cost-of-illness studies for individual countries, no equivalent of Luengo-Fernández exists at country level outside of the 2021 reference year, extrapolation applies a two-factor scaling model grounded in health economics practice:

$$\text{CVD cost (t)} = \text{CVD cost (base)} \times \text{GDP index (base}\rightarrow\text{t)} \times [\text{CHE\%GDP (t)} / \text{CHE\%GDP (base)}]$$

This approach is consistent with the methodology used by the OECD and European Commission for projecting healthcare expenditure in the absence of annual disease-level cost data. It rests on two well-supported premises. First, CVD costs scale with overall economic activity: as nominal GDP grows, wages, unit costs of care, and productivity valuations all rise in approximate proportion. Second, the share of GDP allocated to healthcare, and within it, to CVD, is not static; it is driven by ageing, epidemiological trends, and health system expansion, all of which are captured through the CHE/GDP ratio.

Real GDP growth rates for 2022–2024 are sourced from the World Bank World Development Indicators (April 2025 release). For 2025, rates are drawn from the IMF World Economic Outlook (October 2025). For 2026–2027, country-specific rates apply IMF WEO April 2026 projections, transitioning to IMF and European Commission medium-term potential growth estimates for 2028–2030 and held at long-run potential for 2031–2035. Long-run rates reflect demographic trajectories, productivity convergence, and capital deepening, ranging from approximately 0.9% per annum for Italy to 3.2% per annum for Romania.

Current health expenditure as a percentage of GDP for 2021–2023 is sourced from the World Bank Health Nutrition and Population database. From 2025 onwards, the CHE/GDP ratio is projected forward using an annual drift of +0.10 percentage points per year for Western, Northern, and Southern EU countries and +0.15 percentage points per year for Central and Eastern European countries, consistent with OECD (2019, 2023) long-run healthcare expenditure projections documenting health spending rising by approximately 1.2–1.5 percentage points of GDP across OECD countries between 2015 and 2030, with faster convergence in lower-spending CEE economies. The ratio CHE/GDP(t) / CHE/GDP (base) is applied multiplicatively to the GDP-indexed cost, capturing the changing share of economic output devoted to healthcare independently of GDP growth.

The trajectory reveals three analytically relevant patterns.

The Western/Eastern convergence is real but limited, the gap between the two group means narrows from 2.54 percentage points in 2021 to 1.84 percentage points in 2035, a convergence of 0.70 pp over fourteen years, consistent with the gradual structural catch-up documented in OECD long-run healthcare expenditure projections. Germany (14.20% by 2035) and France (13.60%) anchor the top of the distribution, explaining why these two markets generate the largest absolute CVD cost growth across the projection window despite modest GDP growth rates. Romania (8.30%) and Hungary (8.90%) anchor the bottom, explaining the structurally lower cost per MACE case in these markets relative to their disease burden. Luxembourg is a notable exception within the Western group: its CHE/GDP ratio of 6.80% by 2035 sits well below the Western mean of 11.51%, reflecting the well-documented statistical distortion of

Luxembourg's GDP denominator by its outsized financial sector rather than genuinely lower healthcare intensity. Luxembourg's CVD cost projection is therefore anchored to the Luengo-Fernández 2023 base-year expenditure data rather than derived from its GDP trajectory, as noted in Table 6.5.2.

Country	2021 (€M)	2023e (€M)	2025e (€M)	2035e (€M)	CAGR 2021–23	CAGR 2021–25	CAGR 2025–35	CAGR 2021–35
Austria	8,466	8,098	8,149	10,104	−2.2%	−0.9%	2.20%	1.30%
Belgium	6,797	6,879	7,043	8,756	0.60%	0.90%	2.20%	1.80%
Bulgaria	1,983	1,937	2,059	3,227	−1.2%	0.90%	4.60%	3.50%
Croatia	1,108	1,091	1,161	1,798	−0.8%	1.20%	4.50%	3.50%
Cyprus	309	317	338	486	1.30%	2.30%	3.70%	3.30%
Czechia	5,228	4,952	5,124	7,503	−2.7%	−0.5%	3.90%	2.60%
Denmark	4,392	3,980	4,193	5,536	−4.8%	−1.2%	2.80%	1.70%
Estonia	568	545	556	813	−2.0%	−0.5%	3.90%	2.60%
Finland	4,386	4,627	4,711	5,931	2.70%	1.80%	2.30%	2.20%
France	38,144	37,379	38,277	46,871	−1.0%	0.10%	2.00%	1.50%
Germany	83,400	77,687	78,152	94,611	−3.5%	−1.6%	1.90%	0.90%
Greece	4,315	4,322	4,505	6,206	0.10%	1.10%	3.30%	2.60%
Hungary	3,621	3,248	3,348	5,295	−5.3%	−1.9%	4.70%	2.80%
Ireland	3,442	3,682	3,891	6,024	3.40%	3.10%	4.50%	4.10%
Italy	41,978	40,238	40,881	50,033	−2.1%	−0.7%	2.00%	1.30%
Latvia	750	586	599	906	−11.6%	−5.5%	4.20%	1.40%
Lithuania	1,439	1,401	1,480	2,351	−1.3%	0.70%	4.70%	3.60%
Luxembourg	413	422	431	604	1.10%	1.10%	3.40%	2.80%
Malta	183	193	214	352	2.70%	4.00%	5.10%	4.80%
Netherlands	13,059	12,036	12,348	15,788	−4.0%	−1.4%	2.50%	1.40%
Poland	13,179	15,595	16,549	26,915	8.80%	5.90%	5.00%	5.20%
Portugal	3,772	3,719	3,874	5,193	−0.7%	0.70%	3.00%	2.30%
Romania	6,421	6,053	6,304	10,908	−2.9%	−0.5%	5.60%	3.90%
Slovakia	1,964	1,943	2,029	3,096	−0.5%	0.80%	4.30%	3.30%
Slovenia	1,048	1,075	1,118	1,614	1.30%	1.60%	3.70%	3.10%
Spain	23,960	23,278	24,564	33,191	−1.4%	0.60%	3.10%	2.40%
Sweden	7,211	7,237	7,427	9,674	0.20%	0.70%	2.70%	2.10%
UK †	28,470	27,305	27,999	35,102	−2.1%	−0.4%	2.30%	1.50%
EU27 total	281,536	272,520	279,325	363,786	3.40%	1.62%	3.99%	2.67%
EU27+UK total	310,006	299,825	307,324	398,888	3.40%	1.62%	3.93%	2.63%

† UK figure sourced from Wilkins et al. (2017), adjusted to 2021 EUR using UK healthcare cost inflation indices and 2021 average GBP/EUR exchange rate. 2025e and 2035e figures reflect subsequent GDP and CHE/GDP projections consistent with the model framework described in section 8.5.2.

Table 8.5.2 – Cost of CVD extrapolation by country to 2035

8.5.3 Country-level CVD cost projection assumptions

The two-factor scaling model described in section 8.5.2 is applied using country-specific GDP growth rates and CHE/GDP drift assumptions. This section documents the resulting projection parameters for each of the 28 EU27+UK geographies.

GDP growth rates

For 2022–2024, annual real GDP growth rates are taken from the World Bank World Development Indicators (April 2025 release). For 2025, growth rates are sourced from the IMF World Economic Outlook (October 2025). For 2026–2027, country-specific rates are drawn from the IMF WEO (April 2026). For 2028–2035, growth rates converge to long-run potential as estimated by the IMF and European Commission medium-term projections, reflecting structural factors including demographic trajectories, productivity convergence, and capital deepening. Long-run rates range from approximately 0.9% per annum for Italy and Germany to 3.2–3.5% per annum for Romania and Poland.

CHE/GDP drift assumptions

The CHE/GDP ratio is projected forward from its 2023 observed level using an annual drift of +0.10 percentage points per year for Western, Northern, and Southern EU countries, and +0.15 percentage points per year for Central and Eastern European countries. These assumptions are consistent with OECD (2019, 2023) long-run healthcare expenditure projections, which document faster health spending convergence in lower-spending CEE economies relative to Western European peers.

Resulting projection CAGR 2025–2035

The combined effect of GDP growth and CHE/GDP drift produces the forward CAGR for total CVD costs in each country. Western European countries record a 2025–2035 CAGR of 1.9% to 2.5% for most markets, with Ireland (4.5%) and Malta (5.1%) as notable exceptions reflecting higher near-term GDP growth projections. Eastern and Southern European countries record CAGRs of 3.3% to 5.6%, with Romania (5.6%), Poland (5.0%), Lithuania (4.7%), and Hungary (4.7%) at the upper end, reflecting the combination of faster GDP growth and the higher CHE/GDP drift rate applied to CEE health systems. The full country-level projection parameters are set out in Table 6.5.3 below.

Country	2021 (€M)	2025e (€M)	2035e (€M)	CAGR 2025–35
Austria	8,466	8,149	10,104	2.20%
Belgium	6,797	7,043	8,756	2.20%
Bulgaria	1,983	2,059	3,227	4.60%
Croatia	1,108	1,161	1,798	4.50%
Cyprus	309	338	486	3.70%
Czechia	5,228	5,124	7,503	3.90%
Denmark	4,392	4,193	5,536	2.80%
Estonia	568	556	813	3.90%
Finland	4,386	4,711	5,931	2.30%
France	38,144	38,277	46,871	2.00%
Germany	83,400	78,152	94,611	1.90%
Greece	4,315	4,505	6,206	3.30%
Hungary	3,621	3,348	5,295	4.70%
Ireland	3,442	3,891	6,024	4.50%
Italy	41,978	40,881	50,033	2.00%
Latvia	750	599	906	4.20%
Lithuania	1,439	1,480	2,351	4.70%
Luxembourg	413	431	604	3.40%
Malta	183	214	352	5.10%
Netherlands	13,059	12,348	15,788	2.50%
Poland	13,179	16,549	26,915	5.00%
Portugal	3,772	3,874	5,193	3.00%
Romania	6,421	6,304	10,908	5.60%
Slovakia	1,964	2,029	3,096	4.30%
Slovenia	1,048	1,118	1,614	3.70%
Spain	23,960	24,564	33,191	3.10%
Sweden	7,211	7,427	9,674	2.70%
UK†	28,470	27,999	35,102	2.30%
EU27	310,006	307,324	398,888	3.55%
EU27+UK	338,476	335,323	433,990	3.50%

† UK 2021 base sourced from Wilkins et al. (2017), adjusted to 2021 EUR. Western group 2025–35 CAGR mean: 2.8% (range 1.9–5.1%). Eastern group 2025–35 CAGR mean: 4.3% (range 3.3–5.6%).

Table 8.5.3, Country-level CVD cost projection parameters (€ million)

8.5.4 Evolution of the Total Cost of CVD in EU27+UK

Total CVD costs across the EU27+UK are projected to rise from approximately €300 billion in 2023 to €399 billion in 2035, an increase of 33% over the twelve-year window at a compound annual growth rate of 2.4%. This trajectory reflects the combined effect of nominal GDP growth, the gradual increase in the share of GDP allocated to healthcare, and the demographic ageing of the 55-plus population across most EU27+UK geographies. In real terms, the increase is more modest, the projection does not represent a

deterioration in cardiovascular health but rather the rising economic value of the resources devoted to managing an ageing cardiovascular disease population.

The absolute cost burden remains heavily concentrated in the largest Western European economies. Germany, France, and Italy together account for approximately 52% of the EU27+UK total in 2023 and 48% in 2035, with their combined CVD cost rising from €155 billion to €192 billion over the projection window. Despite their large absolute size, these three countries record among the slowest growth rates, Germany at 1.9% per annum, France and Italy at 2.0%, reflecting mature health systems with limited structural room for rapid CHE/GDP expansion and modest long-run GDP growth trajectories.

Eastern European countries grow substantially faster over the projection window, at a mean CAGR of 4.3% compared with 2.8% for Western Europe. Romania (5.6%), Poland (5.0%), Lithuania (4.7%), and Hungary (4.7%) record the highest growth rates, driven by the combination of above-average GDP growth, faster CHE/GDP convergence toward Western European norms, and in some cases ongoing demographic pressure from high cardiovascular mortality in working-age populations.

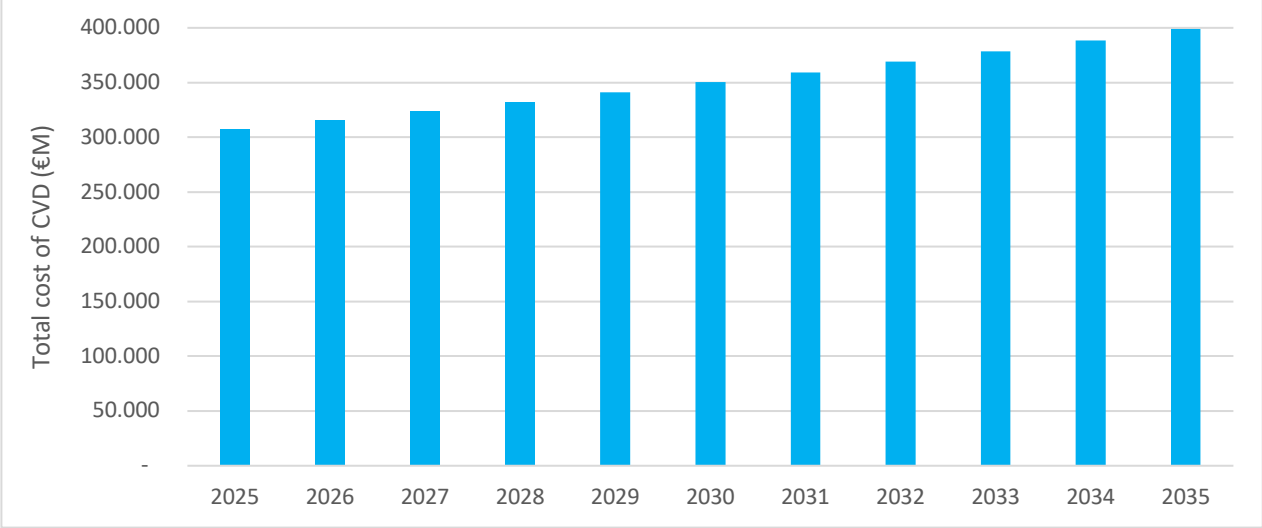

Figure 8.5.4 Total cost of CVD forecast to 2035 (€M)

As a result, the Eastern European share of total EU27+UK CVD cost rises from 14.4% in 2023 to 17.8% in 2035, a gradual but sustained structural shift that increases the relative weight of lower-unit-cost geographies in the aggregate model over time.

8.6 Methodology for Estimating Age-Standardised Cardiovascular Disease (CVD) Mortality Rates

Age-standardised cardiovascular disease (CVD) mortality rates were derived using a harmonised framework designed to ensure comparability across countries and over time. The analysis covers the 27 European Union member states and the UK for three reference years (2001, 2011, and 2021), using mortality rates expressed as deaths per 100,000 population.

The base dataset consists of age-standardised mortality rates for CVD (ICD-10 I00–I99), as reported by Eurostat. These rates are adjusted to a common reference population structure, thereby removing the influence of

differing age distributions across countries. This standardisation is essential in the European context, where variations in population ageing are substantial and would otherwise distort cross-country comparisons.

The calculation of age-standardised mortality rates follows a direct standardisation method, whereby age-specific mortality rates are weighted according to a fixed standard population. Formally, for each country and year, the age-standardised mortality rate (ASMR) is calculated as:

$$ASMR = \Sigma_i (m_i \times w_i)$$

Where:

- m_i = Observed age-specific mortality rate in age group i for the country and reference year in question, calculated as the number of CVD deaths in that age group divided by the mid-year population in that age group, expressed per 100,000
- w_i = Weight assigned to age group i, defined as the proportion of the standard reference population falling within that age group; the standard population used throughout this analysis is the 2013 European Standard Population (ESP2013) as published by Eurostat, which assigns fixed proportional weights across 19 five-year age bands summing to 1.0

The sum across all age groups yields the overall mortality rate per 100,000 population, adjusted to the standard age structure. This ensures that differences between countries reflect underlying epidemiological conditions and health system performance, rather than demographic composition.

In this analysis, the reported ASMR values were used directly without recalculation, ensuring consistency with official national and international reporting standards. However, understanding the underlying calculation is critical, as it underpins the comparability of the dataset and enables its use as a foundation for further derived metrics. To support downstream modelling, including estimation of premature mortality and hospitalisation rates, the age-standardised mortality rate was treated as the central anchor variable. This reflects its role as a composite indicator of both disease burden and system effectiveness. Higher mortality rates generally indicate a combination of higher incidence, greater severity, and/or less effective prevention and treatment.

Regional stratification was applied to enhance interpretability. Countries were grouped into Western/Nordic, Southern, Central, and Eastern European clusters based on observed mortality patterns and known epidemiological characteristics. Western and Nordic countries typically exhibit lower mortality rates, reflecting strong primary prevention, early diagnosis, and effective chronic disease management. In contrast, Central and Eastern European countries show persistently higher mortality, associated with higher prevalence of key risk factors such as hypertension, smoking, and dyslipidaemia, as well as gaps in treatment coverage.

Temporal trends were analysed by comparing ASMR values across the three reference years. Between 2001 and 2011, most countries experienced substantial declines in mortality, driven by improvements in acute cardiovascular care, widespread use of lipid-lowering and antihypertensive therapies, and reductions in

smoking prevalence. Between 2011 and 2021, however, the rate of decline slowed, with some countries showing stagnation. This reflects the increasing influence of metabolic risk factors, including obesity and diabetes, which are more resistant to rapid intervention.

While age-standardisation provides a robust basis for comparison, certain limitations remain. Variations in death certification practices and coding accuracy may introduce minor inconsistencies. Additionally, mortality rates capture only fatal outcomes and do not reflect the full burden of non-fatal cardiovascular disease, which remains substantial and, in many countries, is increasing.

8.7 Methodology for Estimating CVD hospitalisation Rates

Cardiovascular disease (CVD) hospitalisation rates were estimated for the EU27 and the UK using a model-based approach, designed to enable consistent cross-country comparison in the absence of harmonised administrative data covering all countries. While hospital discharge and admission data exist at national level, differences in definitions, coding practices, and reporting standards limit their comparability. A standardised estimation framework was therefore applied.

The methodology is anchored in the established relationship between disease burden and healthcare utilisation, using age-standardised mortality rates (ASR) as a proxy for underlying CVD burden. ASR reflects both the prevalence and severity of disease, as well as the effectiveness of prevention and treatment pathways, and provides a consistent basis for cross-country comparison.

A reference calibration was derived from the UK, where high-quality, standardised hospital admission data are available. Based on Office for Health Improvement and Disparities (OHID) data, CVD hospitalisation rates in England stabilised at approximately 390–415 admissions per 100,000 population in the post-pandemic period. A midpoint value of 400 per 100,000 was selected as the anchor. This was combined with the estimated UK age-standardised CVD mortality rate for 2023 (253.8 per 100,000), yielding a mortality-to-hospitalisation coefficient:

$$K = \frac{400}{253.8} = 1.58$$

This coefficient implies that, on average, there are approximately 1.6 hospital admissions per CVD death in the reference system.

Country-level hospitalisation rates were then estimated using the following relationship:

$$\text{Hospitalisation rate}_c = ASR_{c,2023} \times 1.58 \times S_c$$

Where S_c represents a system adjustment factor reflecting differences in healthcare delivery and utilisation across regions. Adjustment factors were applied as follows: Western and Nordic Europe (0.90), Southern Europe (0.95), Central Europe (1.05), and Eastern/Baltic Europe (1.15). These factors account for variation in admission thresholds, outpatient versus inpatient management, repeat hospitalisations, and disease severity at presentation.

This approach ensures that hospitalisation estimates reflect both epidemiological burden and health system behaviour, while maintaining internal consistency across countries.

The resulting estimates should be interpreted as comparative proxies of hospitalisation intensity, rather than exact administrative measures. While absolute values may differ from national statistics, the methodology preserves relative differences and provides a robust basis for cross-country analysis of cardiovascular healthcare burden.

8.8 Methodology for High Cholesterol Prevalence Estimation (EU27+UK)

Country-level raised cholesterol prevalence was sourced from the NCD Risk Factor Collaboration (NCD-RisC) 2020 analysis (Nature 582:73–77), which provides age-standardised estimates of total cholesterol ≥5.0 mmol/L for all EU27 member states and the UK, derived from a pooled analysis of 1,127 population-based studies covering the period 1980–2018.

WHO Global Health Observatory country estimates were used as a cross-reference for countries where NCD-RisC confidence intervals were wide. Prevalence rates were applied to national adult population denominators for the 55+ age cohort, sourced from Eurostat 2023 demographic projections, to generate absolute case counts for the reference years 2023, 2025, and 2035.

The eligibility threshold of elevated total cholesterol (≥5.0 mmol/L) is used as the risk factor criterion for Phytosterols and Beta-Glucan. Country-level prevalence estimates are applied to the population aged 55 and above to derive the intervention-eligible population used in the model. No adjustment is made for statin or other lipid-lowering treatment status; therefore, the full high-total-cholesterol population aged 55 and above forms the eligible population denominator for the Phytosterol and Beta-Glucan analyses.

8.9 Methodology for Estimating Familial Hypercholesterolaemia Prevalence (EU27+UK)

Familial hypercholesterolaemia (FH) is a monogenic disorder characterised by severely elevated LDL-cholesterol from birth and substantially higher lifetime risk of premature cardiovascular disease. Despite representing a small share of the total high cholesterol population, adults with FH aged 55 and above are included in the eligible population denominator for Phytosterols and Beta-Glucan on the basis that their elevated LDL-C profile is directly targeted by both interventions and that the EU-authorised health claims apply to LDL-C reduction without restriction to aetiology.

8.9.1 Prevalence rate derivation

Country-level FH prevalence rates are derived from Vallejo-Vaz et al. (2018),[71] the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC) overview of FH status in over 60 countries,

[71] Vallejo-Vaz AJ et al. on behalf of the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC) (2018). Overview of the current status of familial hypercholesterolaemia care in over 60 countries. Atherosclerosis, 277:234–255.

supplemented by the foundational EAS Consensus Panel estimates of Nordestgaard et al. (2013) for countries where no national registry or population-based data were reported. [72]

Country	FH prevalence rate	Total FH population	FH aged 55+	Evidence basis
Austria	0.30%	27,334	9,176	EAS Consensus / FHSC
Belgium	0.32%	37,854	12,006	EAS Consensus
Bulgaria	0.35%	24,011	8,009	EAS Consensus
Croatia	0.36%	13,718	4,871	FHSC est. ~15,000 HeFH
Cyprus	0.30%	2,825	687	EAS Consensus
Czechia	0.40%	44,069	14,675	MEDPED network, 1:250
Denmark	0.46%	27,508	8,808	Copenhagen GPS, 1:217
Estonia	0.23%	3,168	1,004	NEMC registry, 1:440
Finland	0.25%	14,101	4,879	Founder mutations 1:500; broader est. 1:200
France	0.40%	274,633	89,177	French FH Registry, 1:250
Germany	0.34%	289,706	106,952	DETECT study, 1:295
Greece	0.40%	41,281	14,685	HELLAS-FH / EAS est., 1:250
Hungary	0.34%	32,792	10,252	EAS Consensus
Ireland	0.39%	20,504	5,168	National screening, 1:259
Italy	0.30%	176,853	66,833	EAS Consensus (DLCN-based est. conservative)
Latvia	0.40%	7,452	2,491	Latvian FH Registry, 1:250 assumed
Lithuania	0.50%	14,302	4,661	National programme, 1:200
Luxembourg	0.30%	2,061	546	EAS Consensus
Malta	0.30%	1,661	495	FHSC est. ~1:300
Netherlands	0.45%	81,219	26,253	StOEH cascade screening, 1:222
Poland	0.40%	153,525	46,051	Meta-analysis 6 studies, 1:250
Portugal	0.31%	32,154	11,749	EAS Consensus
Romania	0.35%	65,911	19,884	EAS Consensus
Slovakia	0.34%	18,773	5,453	EAS Consensus / MEDPED-Slovakia
Slovenia	0.20%	4,242	1,423	Universal genetic screening, 1:500
Spain	0.33%	160,426	53,599	SAFEHEART est., 1:303
Sweden	0.36%	38,541	11,825	EAS Consensus
UK	0.30%	209,700	62,663	NICE / EAS est., 1:300
EU27	**0.35%**	**1,610,624**	**541,612**	
EU27+UK	**0.35%**	**1,820,324**	**604,275**	

Table 8.9.1, Country-specific FH prevalence rates and estimated FH population, 2025

Note: EU27 and EU27+UK population figures represent the sum of the respective country-level estimates. FH prevalence rates represent the unweighted average of the country-level prevalence rates.

[72] Nordestgaard BG et al. (2013). Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. European Heart Journal, 34(45):3478–3490.

Where country-specific data from national registries, cascade screening programmes, or population studies were available in Vallejo-Vaz et al. (2018), these are applied directly.

For twelve countries where no national estimate was available in Vallejo-Vaz et al. (2018), Belgium, Bulgaria, Cyprus, Hungary, Italy, Luxembourg, Malta, Portugal, Romania, Slovakia, Sweden, and Austria, the EAS Consensus Panel general estimate of 1:300 to 1:500 is applied, with individual rates set within the 0.30–0.35% range consistent with the central EAS estimate from Nordestgaard et al. (2013). All rates are held constant across the 2023–2035 projection window, consistent with the assumption that FH prevalence is genetically determined and does not change materially over the projection horizon. The full country-level FH prevalence rates applied in the model are set out in Table 8.9.1.

8.9.2 Population sizing and model integration

The FH-positive population in each country is derived by applying the country-specific prevalence rate to the total national population, then apportioning to the 55-plus age cohort using the same age-band proportioning methodology applied to all other risk factor populations as described in section 8.3.4. Across the EU27+UK in 2025, the FH-positive population aged 55 and above totals approximately 604,000 adults, representing 0.7% of the combined high total cholesterol and FH eligible population of approximately 83.7 million used as the Phytosterols and Beta-Glucan denominator. The FH increment is modest in aggregate but ensures that a clinically important and high-risk subgroup is not excluded from the eligible population without justification.

FH patients are not separately modelled with a higher RRR despite their elevated baseline cardiovascular risk. The base-case RRR of 7% for Phytosterols and 6.4% for Beta-Glucan is applied uniformly to the combined eligible population including FH patients. This is a conservative assumption: the absolute risk reduction per FH patient is likely higher than for the general hypercholesterolemic population given their higher baseline event rate, meaning the model understates the economic return attributable to the FH subgroup. Should a subsequent iteration of the model incorporate a separate, higher RRR for the FH subgroup, the proportional impact on aggregate net benefit would be modest given the FH population represents less than 1% of the combined eligible denominator.

8.10 Methodology for Estimating the MACE Incidence Baseline (ER)

8.10.1 Definition and scope

The event rate baseline (ER) is the foundational clinical parameter linking the eligible population to the volume of avoidable events in the cost-savings model. It represents the proportion of total MACE incidence occurring in the 55-plus population in each country and year, and serves as the scaling factor from which the absolute risk reduction (ARR) is derived when multiplied by the intervention-specific relative risk reduction (RRR):

$$ARR = ER \times RRR$$

Avoidable events = ARR × Eligible population

A higher ER baseline produces a higher ARR at the same RRR, yielding more avoidable events per supplement user and a lower NNT. The ER baseline is an important determinant of modelled supplementation efficiency; however, geographic variation in ER is relatively narrow, ranging from approximately 84% to 92% across the 28 EU27+UK geographies.

For the three interventions modelled here, the RRR parameters applied to the ER baseline are 5% for Omega-3 EPA+DHA at 1g/day (9% at 2g/day), 7% for Phytosterols at 1.5g/day (12% at 3g/day), and 6.4% for Beta-Glucan at 3g/day, as set out in Section 7.1.2. The ER baseline is identical across all interventions within each country; differences in avoidable event volumes between interventions reflect solely differences in RRR and eligible population size. The full efficacy parameter specification for both scenarios is set out in Table 5.2.2.

8.10.2 Epidemiologic Data Source

The MACE incidence baseline is sourced from the IHME Global Burden of Disease 2023 study (GBD 2023), which provides country-level estimates of cardiovascular disease incidence disaggregated by age group, sex, and ICD-10 category. The CVD incidence figure applied in the model is the aggregate incident case count for ICD-10 codes I00–I99 across all ages and in the population aged 55 and above in each country for the 2023 reference year. The ER baseline is calculated as the ratio of 55-plus incident cases to total incident cases, expressing the proportion of annual CVD incidence occurring in the 55-plus population. The same country-specific ER baseline is applied across the three interventions; differences in avoidable event volumes arise from the intervention-specific RRRs and eligible population sizes.

The IHME GBD CVD incidence aggregate (I00–I99) encompasses all cardiovascular conditions including ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, atrial fibrillation, hypertensive heart disease, and other circulatory conditions. It is a broader definition than the clinical MACE endpoint, which conventionally covers myocardial infarction, stroke, and cardiovascular death, used in the RCTs from which the intervention RRRs are derived. This definitional breadth is a deliberate modelling choice consistent with the primary prevention orientation of the model and the preventive supplementation context of this model.

8.10.3Quantitative basis

Across the EU27+UK in 2023, the IHME-derived CVD incidence totals approximately 5.99 million cases across all ages, of which approximately 5.39 million, 90%, occur in the population aged 55 and above, against a 55-plus population of 173.1 million. Country-level ER baselines range from approximately 84.4% in Cyprus to 92.0% in Finland, reflecting the consistent concentration of MACE incidence in the 55-plus cohort across all 28 geographies. The narrow range of approximately 84% to 92%, compared with the 17 percentage point spread in the prevalence-based ER used in the previous model version, confirms that the 55-plus age group accounts for the substantial majority of new cardiovascular events in every EU27+UK market and that geographic variation in supplementation efficiency is driven primarily by variation in healthcare unit costs and supplement retail prices rather than by variation in the ER baseline itself.

The ER baseline is projected forward across the 2025–2035 window by holding the IHME 2023 incidence ratio constant across the projection period. This is consistent with the assumption that the proportional concentration of MACE incidence in the 55-plus cohort does not change materially over the projection horizon, which is supported by the demographic stability of the age-incidence relationship in the IHME GBD dataset across recent projection cycles. To the extent that the share of MACE incidence occurring in the 55-plus population may increase over the projection window, driven by continued demographic ageing of the EU27+UK population, this assumption is conservative and produces a lower-bound estimate of the ER baseline and therefore of avoidable events across the projection window.

Figure 8.10.1 charts the MACE incidence-based ER baseline across all 28 EU27+UK geographies in 2023, expressed as the proportion of total CVD incidence occurring in the 55-plus population. The range spans approximately 7.6 percentage points from 84.4% in Cyprus to 92.0% in Finland, a materially narrower distribution than the 17-percentage-point prevalence-based range documented in the previous model version. The distribution does not follow a clear Eastern/Western geographic gradient, reflecting the fact that the age-concentration of MACE incidence is driven primarily by demographic age structure within the 55-plus cohort rather than by cardiovascular risk factor profiles or healthcare system characteristics. Finland, Sweden, Portugal, Latvia, and Lithuania record the highest ER baselines, while Cyprus, Malta, Ireland, Luxembourg, and Slovakia record the lowest, a pattern that broadly corresponds to the relative weight of the oldest age bands within the 55-plus cohort in each geography.

The interaction between the ER baseline and cost per incident case influences gross societal cost savings and the geographic distribution of net benefit. Finland records the highest ER baseline at 92.0%, while Ireland records the highest total societal cost per incident MACE case at €110,990 in 2025. The two parameters, incidence concentration and unit cost, interact differently across geographies, producing a geographic net benefit distribution that does not map straightforwardly onto either the ER baseline or the cost-per-case distribution alone, as documented in section 5.5.3.

8.10.4 Relationship to clinical trial MACE definition

The RRRs applied in this model are derived from clinical trials and meta-analyses in which the MACE endpoint was defined as the composite of myocardial infarction, stroke, and cardiovascular death, corresponding primarily to IHD and cerebrovascular incident cases. The IHME I00–I99 aggregate used as the ER baseline is broader than this clinical MACE definition, incorporating incident cases with cardiovascular conditions beyond those directly captured in the trial composite endpoint. The practical effect is that the ER baseline captures a wider set of new cardiovascular events than a strict IHD-plus-stroke incidence figure would produce. For Austria in 2023, the IHME aggregate yields an ER of 89.8% against an IHD-plus-stroke-only ER of approximately 71.3%, meaning the model generates higher ARR and avoidable event volumes than a narrower definition would produce.

This design choice is consistent with the preventive supplementation context of the model. Adults meeting the cardiovascular risk factor eligibility criteria in this model (elevated triglycerides for Omega-3; elevated total cholesterol for Phytosterols and Beta-Glucan) face elevated cardiovascular risk across the full I00–I99 spectrum and are plausible beneficiaries of lipid-lowering and triglyceride-lowering supplementation

regardless of whether their specific condition maps directly to the trial composite endpoint. The alternative, restricting the ER baseline to IHD-plus-stroke incident cases only, would exclude individuals with hypertensive heart disease, atrial fibrillation, and peripheral vascular disease who face elevated MACE risk and for whom LDL-C reduction is clinically indicated under standard cardiovascular risk management guidelines. The broader IHME aggregate is therefore the more appropriate denominator for a population-level prevention model targeting the at-risk population defined by established cardiovascular risk factor thresholds. Readers who prefer a narrower ER definition restricted to IHD-plus-stroke incidence should apply a scalar of approximately 0.77 to the avoidable event and gross societal cost savings figures in Section 7; net benefit remains positive across all 28 EU27+UK geographies for all three interventions under this assumption.

8.11 Methodology for Estimating Annual CVD Cost Components by Country (EU27+UK)

8.11.1 Purpose

Three cost components feed the gross societal cost savings calculation throughout this model: direct health and social care (H&SC), informal care, and productivity losses. This section documents how each is derived from the total projected CVD cost and how the resulting per-case figures are applied in the net benefit analysis in Section 7.

8.11.2 Methodology

The component shares are derived from the Luengo-Fernández et al. (2023) base-year dataset, which reports total CVD costs for each EU27 member state and the UK for the reference year 2021 disaggregated into H&SC, informal care, and productivity components. For each country, the proportional share of each component in the 2021 total is calculated as:

H&SC share = H&SC cost 2021 / Total CVD cost 2021 Informal care share = Informal care cost 2021 / Total CVD cost 2021 Productivity share = Productivity cost 2021 / Total CVD cost 2021

These three shares sum to 1.0 for each country by construction. They are held constant across the 2023–2035 projection window on the assumption that the relative structure of CVD costs, the proportional split between direct healthcare expenditure, informal care burden, and productivity loss, does not change materially over the projection horizon. While secular trends in healthcare delivery, informal care provision, and labour force participation could alter these proportions over time, no reliable EU-wide evidence base exists to project component-level cost shares forward with sufficient precision to justify departing from the 2021 base-year structure.

The annual cost for each component in each country and year is then derived by applying the country-specific 2021 share to the projected total CVD cost from section 8.5:

H&SC cost (€M) = Total CVD cost (€M, projected) × H&SC share 2021 Informal care cost (€M) = Total CVD cost (€M, projected) × Informal care share 2021 Productivity cost (€M) = Total CVD cost (€M, projected) × Productivity share 2021

This approach ensures that the component-level cost estimates inherit the full GDP-indexed and CHE/GDP-adjusted trajectory of the total cost projection while maintaining the country-specific cost structure observed in the 2021 source data. All three component values sum exactly to the projected total in every country and year by construction.

8.11.3 Results

At the EU27+UK aggregate level in 2023, the H&SC component accounts for approximately €163 billion, representing 54.5% of the total projected CVD cost of €300 billion. Informal care accounts for approximately €82 billion (27.3%) and productivity losses for approximately €55 billion (18.4%). These aggregate shares mask substantial country-level variation. The H&SC share ranges from 33.6% in Latvia to 66.4% in the Netherlands, reflecting fundamental differences in healthcare system structure, institutional care versus family-based care norms, and the relative labour market value assigned to cardiovascular productivity losses across EU27+UK member states. Eastern European countries consistently show lower H&SC shares and higher informal care shares, reflecting care delivery systems that rely more heavily on unpaid family care than on formal health system infrastructure.

8.11.4 Use in the model

The cost per incident MACE case for each component, H&SC, informal care, and productivity, is then derived by dividing the annual component cost in euros by the number of incident MACE cases across all ages in each country and year, sourced from the IHME GBD 2023 dataset as described in §8.10. This produces the country- and year-specific per-case cost figures that are applied to the volume of avoidable events in the net benefit calculation throughout Section 7. The full country-level component shares are derived from Luengo-Fernández et al. (2023).