The burden of LDL-cholesterol-driven atherosclerotic cardiovascular diseases

CONTRACT RESEARCH REPORT
March 2026

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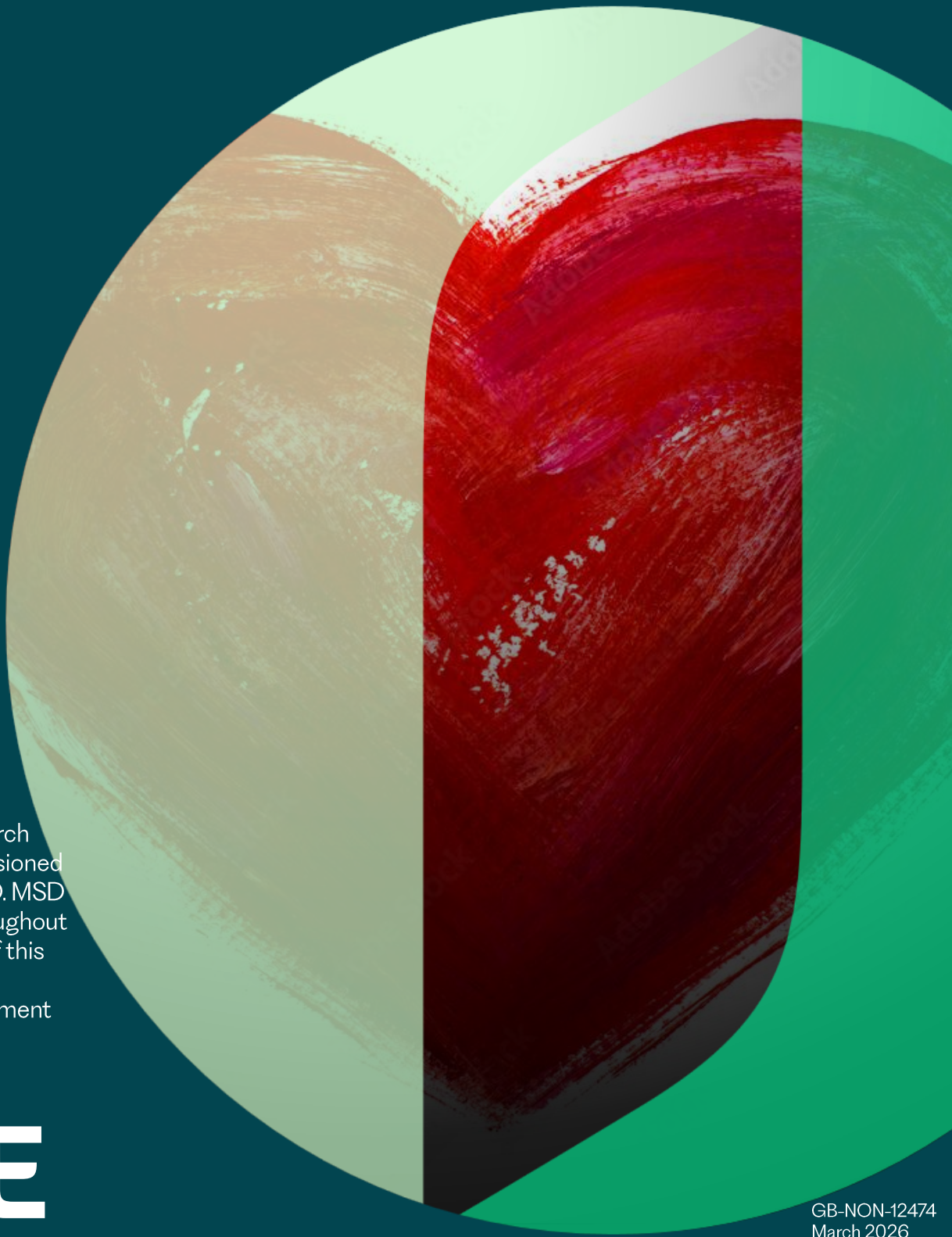

This contract research report was commissioned and funded by MSD. MSD was consulted throughout the development of this report and provided opportunity to comment and input prior to publication.

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List of acronyms and abbreviations

ASCVD: Atherosclerotic cardiovascular disease

CVD: Cardiovascular disease

DALY: Disability-adjusted life-year

GBD: Global Burden of Disease

GDP: Gross domestic product

GHED: Global Health Expenditure Database

HCA: Human capital approach

HCRU: Healthcare resource utilisation

IHD: Ischemic heart disease

IHME: Institute for Health Metrics and Evaluation

IS: Ischemic stroke

LDL-C: Low-density lipoprotein cholesterol

LLT: Lipid-lowering therapy

MACE: Major adverse cardiovascular event

MALE: Major adverse limb event

NCD: Noncommunicable disease

OECD: Organisation for Economic Co-operation and Development

PAD: Peripheral arterial disease

PAF: Population-attributable fraction

PD: Polyvascular disease

PPP: Purchasing Power Parity

TMREL: Theoretical minimum risk exposure level

YLD: Years lived with disability

YLL: Years of life lost

WHO: World Health Organisation

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Executive Summary

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of morbidity and mortality globally (Nedkoff et al., 2023; Rout et al., 2024; Ji et al., 2025), responsible for substantial health and economic burdens on patients, health systems, and wider society. There has been an upward trend in the years of life lost due to ASCVDs (Institute for Health Metrics and Evaluation, 2024, p.202), and a notable increase in ASCVD prevalence in the working-age population (Li et al., 2024). Cumulative exposure to elevated low-density lipoprotein cholesterol (LDL-C) is a primary risk factor for ASCVD (Ference et al., 2017; Rikhi and Shapiro, 2022), and its effective management presents a significant opportunity to reduce the health and economic burden associated with ASCVD.

This report quantifies the health and economic burden of ASCVD, with a focus on the share attributable to elevated LDL-C. Using data from the Global Burden of Disease (GBD) Study and WHO Global Health Expenditure Database (WHO, 2023; Institute for Health Metrics and Evaluation, 2024), and subject to data limitations, we estimate that ASCVD accounts for approximately **261 million disability-adjusted life years (DALYs)** and **Int$680[1] billion in direct healthcare costs** annually worldwide, roughly equivalent to the annual GDP of Sweden or Argentina (IMF, 2025). This could reach up to Int$1.4 trillion — 0.7% of global gross domestic product (GDP) — when considering the impact of indirect costs, such as those associated with productivity losses and informal care.

We also estimate, subject to similar data limitations, that **LDL-C contributes up to one-third of this burden**, equating to **Int$230 billion in direct costs** and up to **Int$480 billion in total direct and indirect costs, or roughly the GDP of Vietnam** (IMF, 2025). These figures highlight the scale of the burden of ASCVD, and the relative contribution of elevated LDL-C to this overall burden. Whilst we suggest that much of these burdens could, in theory, be avoided through some a combination of prevention, early detection and treatment, we do not recommend or evaluate specific strategies, and therefore our estimates are independent of the costs of such interventions.

In addition to this global estimate, we estimate the health and economic burdens of ASCVD, and the contribution of LDL-C to these burdens, in nine nations (US, Canada, UK, Netherlands, France, Germany, Spain, Italy, and Japan) in more detail. Ischemic heart disease was the most costly disease in most countries, and indirect costs were often greater than the direct costs, driven by time and productivity losses due to mortality. The burdens of informal caring were also substantial, highlighting the spillover effects of ASCVD beyond patients and the healthcare system. As in the global estimate, we find that up to one-third of the health and economic burdens of ASCVD are associated with elevated LDL-C.

The report also examines the relative contribution of different ranges of LDL-C to the overall burden of ASCVD. Using the United Kingdom as an illustrative example, we find that moderately elevated—i.e. those considered 'near optimal/above optimal', 'borderline high', and 'high' (Pappan, Awosika and Rehman, 2025)—LDL-C categories (2.6-4.1 mmol/L or 100.5-158.5 mg/dL) contribute more to overall costs than higher-risk categories due to the greater prevalent population in this range. This suggests that early interventions targeting LDL-C reductions in this 'moderately elevated' group could yield significant economic benefits.

[1] We used PPP-adjusted international dollars (Int$) for cross-country aggregation to ensure comparability of real resource use in our global analysis. Conversely, we used nominal US dollars (US$) for country-specific estimates to reflect actual expenditures and facilitate interpretation by national stakeholders.

Given the substantial but avoidable health and economic burdens attributable to elevated LDL-C, there is clear imperative for better prevention and management of this risk factor. There is strong clinical evidence and treatment guidelines advocating for LDL-C reduction (Aygun and Tokgozoglu, 2022; Kang et al., 2025), but implementation gaps persist. Lifestyle interventions can also be effective, but often fall short due to adherence challenges (Wadhera et al., 2016; Gant et al., 2018), and there is evidence that lipid-lowering therapies (LLTs) remain underutilised (Şener and Tokgözoğlu, 2023).

Using the available data, we present an estimate of the scale of the global burden of ASCVD. This represents an urgent call to action to adopt strategies that could reduce the burden of ASCVD on patients, health systems and society.

1 Background

1.1 Motivation

There is growing recognition of the 'value of prevention' in improving population health, reducing health system costs, and strengthening economic productivity. McKinsey (2020), for example, estimates that prevention in the form of cleaner and safer environments, healthier behaviours, and access to vaccines and preventative medicines could add US$12 trillion to annual global gross domestic product (GDP) by 2040. They estimate each dollar invested in prevention can return $2-4 in wider economic benefits, not considering direct savings to healthcare systems. Specifically in the context of non-communicable diseases (NCDs), the World Health Organization (WHO) estimates that an additional investment of $3 per person could save over 12 million lives, prevent 28 million cases of heart attack and stroke, add more than 150 million healthy years of life, and generate a trillion dollars in economic benefits (WHO, 2025).

OHE shows that investments in prevention are typically more efficient than equivalent investments in treatment; they estimate that in the UK an additional year of good health via prevention costs an estimated £3,800, compared to £13,500 via treatment (Hampson et al., 2023; El Banhawi et al., 2024).

Despite these potential returns, however, among EU countries, only 5.5% of current healthcare expenditures is allocated to preventive healthcare (Eurostat, 2025).

1.2 Prevention in the context of atherosclerotic cardiovascular disease

Atherosclerotic cardiovascular disease (ASCVD) is a consequence of arterial plaque build-up (Steen Carlsson et al., 2023; Barquera et al., 2015), and refers to three main diseases - ischemic heart disease (IHD), ischemic stroke (IS), and peripheral arterial disease (PAD) (Ji et al., 2025; Li et al., 2024; Nedkoff et al., 2023). IHD and IS, in particular, are leading global causes of morbidity and mortality (World Health Organization, 2024; Ji et al., 2025). Polyvascular disease — the presence of atherosclerosis in two or more vascular beds (i.e. being multimorbid in any of these ASCVDs) — is likewise a significant contributor to ASCVD's overall burden (Tannu et al., 2024). Indeed, 30-70% of people with ASCVD have polyvascular disease, and each additional vascular bed affected by ASCVD is associated with an increased risk of major adverse cardiovascular events (MACEs) and major adverse limb events (MALEs) (Tannu et al., 2024).

ASCVD therefore imposes significant costs on health care systems; while few studies have captured the indirect costs owed to ASCVD, those that have aimed to do so have found significant impacts on productivity (Steen Carlsson et al., 2023). These productivity costs are increasing in relevance as ASCVD prevalence increases within the working age population (Li et al., 2024).

Cumulative exposure to low-density lipoprotein cholesterol (LDL-C) is a primary risk factor for ASCVD (Ference et al., 2017; Rikhi and Shapiro, 2022). However, there are a number of interventions that can be used to effectively manage LDL-C levels and, therefore, lower ASCVD risk (Mhaimeed et al., 2024). Lowering LDL-C levels has also been shown to reduce the relative risk of MACEs associated with ASCVD, including strokes, myocardial infarctions, and cardiovascular deaths (Tannu et al., 2024; Sabatine et al., 2018). This suggests that investing in better detection and management of elevated

LDL-C could lead to substantial reductions in morbidity, mortality, and health system costs.

1.3 Report outline

As a first step in demonstrating such a value case, this report quantifies the total health and economic burden of ASCVD, and subsequently the share of this burden LDL-C contributes towards, in terms of direct and indirect costs to health systems, unpaid caregivers, and national economies, as well as the health burdens on patients.

We start by describing global trends in the prevalence and burden of ASCVD. We go on to describe a high-level estimate of global healthcare costs and disability-adjusted life years (DALYs)[2] associated with ASCVD, along with an estimate of the LDL-C-related burden. Global estimates are unavoidably approximate, given data gaps and inconsistencies in how different countries measure or report costs and burdens, but we estimate that the annual global burden of ASCVD is in the range of a quarter of a billion DALYs and two-thirds of a trillion dollars in direct healthcare costs each year. We present this as an estimate of the rough magnitude of the burden rather than a precise estimate.

We also find that LDL-C contributes towards up to a third of this burden. We go on to take a closer look at a subset of countries with richer data availability to explore the direct and indirect burdens of ASCVD and the share of potentially preventable burdens in more detail.

[2] DALYs are calculated by aggregating the years of life lost to a disease and the years lost due to disability. DALYs are commonly used in academic literature as a measure of disease burden because it considers reduced health states before death in addition the decline in life expectancy caused by a disease (Kim et al., 2022)

2 Trends in ASCVD

ASCVD is the primary driver of cardiovascular-related morbidity and mortality, and data suggest that its burden is increasing (Rout et al., 2024; Ji et al., 2025). Due to the structure of available data in epidemiological resources, ASCVD is typically studied through its individual manifestations — particularly, IHD, IS, and PAD (Li et al., 2024; Ji et al., 2025; Nedkoff et al., 2023). Nevertheless, trends across these subtypes reveal a significant and growing burden.

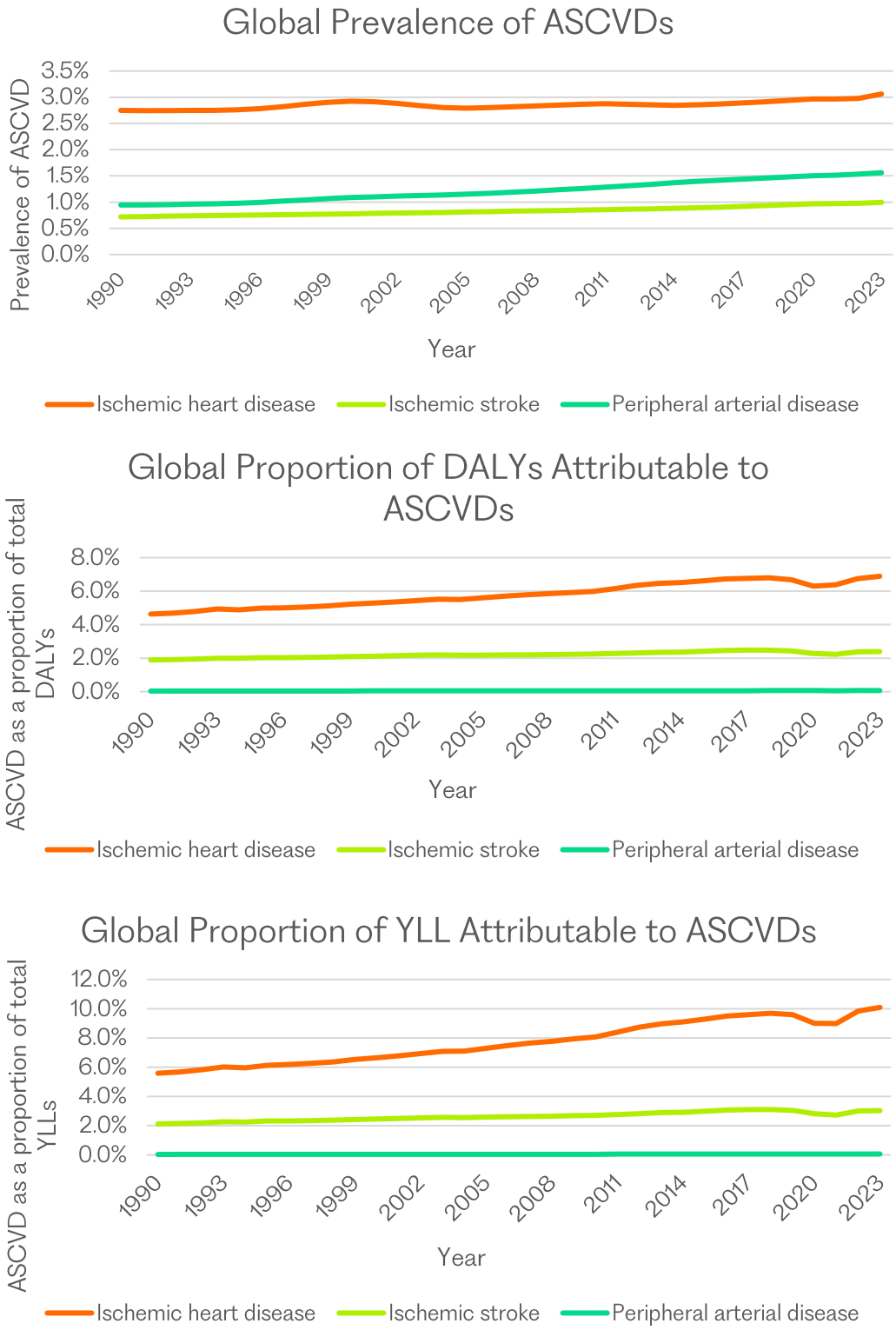
From 1990 to 2021, the absolute global prevalence, mortality, and DALYs associated with ASCVD increased by 115.6%, 63.9%, and 55.6%, respectively — with this burden being predominantly driven by metabolic and lifestyle factors (Ji et al., 2025; Li et al., 2024). Figure 1 presents trends in global ASCVD prevalence, DALYs, and years of life lost (YLL), revealing that, despite a slight reversal in recent years, the prevalence and burden of ASCVD remain historically high.

While ASCVD primarily affects older adults, its impact on younger populations is increasing. Between 1990 and 2019, the prevalence of IHD, IS, and PAD among those aged 20-54 rose by 20.6%, 11.5%, and 7.4%, respectively — contrasting with a decline in prevalence among individuals over 55 (Li et al., 2024). Indeed, in 2019, 15.9%, 23.8%, and 13.65% of global IHD, IS, and PAD cases, respectively, were observed in adults under the age of 55 (Li et al., 2024). Notably, early onset of ASCVD increases lifetime risk of mortality and may impose a prolonged burden on healthcare systems (Ji et al., 2025; Li et al., 2024).

Ultimately, these trends highlight that ASCVD's impact is increasing in magnitude, even as it is already a primary contributor to world morbidity and mortality. The increasing prevalence of ASCVD in the working-age population is particularly of note, given that early development of ASCVD increases lifetime risk of mortality (Li et al., 2024), and a labour force sidelined by a reduced health-related quality of life could yield significant economic impacts — particularly in ageing societies where growth is dependent on an economically active working-age population. Central to this increased impact are metabolic and lifestyle factors (Ji et al., 2025; Li et al., 2024), suggesting that much of ASCVD's growing burden could be prevented altogether.

These trends motivate this report's aim, underscoring the importance of understanding the full socioeconomic burden of ASCVD, as well as how much of that burden is owed to elevated LDL-C, a primary risk factor for ASCVD that is largely preventable.

Figure 1 Trends in ASCVD prevalence, DALYs, and YLL



All data is from the GBD 2023 (Institute for Health Metrics and Evaluation (IHME), 2024).

3 The estimated global burden of ASCVD

To develop an indicative estimate of the global burden of ASCVD, we used data from the WHO Global Health Expenditure Database (GHED), the 2023 Global Burden of Disease (GBD) Study, and an academic paper estimating NCD expenditure in OECD countries (Institute for Health Metrics and Evaluation, 2024; WHO, 2023; Grimshaw, Bourke and Blakely, 2025).

For countries included in our country-specific analyses (section 5 of this report), we used the ASCVD cost estimates generated as part of our analysis. However, given the absence of data on the specific proportion of healthcare expenditure directed to ASCVD in other countries, we took a four-step approach to estimate this sum for other countries, relying on country-specific data on disease burden on health expenditure:

1. First, we estimated the current health expenditure by multiplying country-specific estimates of per-capita health spending by population size to estimate total direct healthcare spending by country, adjusted for differences in purchasing power to give purchasing-power parity (PPP) adjusted 2024 international dollars (Int$) (WHO, 2023). Using Grimshaw, Bourke and Blakely (2025) as a guide, we excluded expenditure on long-term care, preventative care and governance and health system and financing administration.

2. As a first approximation of the share of total healthcare expenditure attributable to ASCVDs, we assumed the share of ASCVD expenditure would be roughly approximate to the share of total DALYs associated with ASCVD sub-diseases (IHD, IS, and PAD). Specifically:

$$ASCVD\ Exp.Share \cong \frac{ASCVD\ DALYs}{All\ DALYs}$$

3. To account for observed imbalances between relative DALY burden and relative expenditure on all non-communicable diseases (NCDs), we adjusted the share from step 2 by the ratio of the relative share of expenditure on all NCD to the relative share of DALYs attributable to all NCDs. That is:

$$Adjusted\ ASCVD\ Exp.Share \cong ASCVD\ Exp.Share \times \frac{Relative\ NCD\ Expenditure}{NCD\ DALYs/All\ DALYs}$$

By doing this, we assumed the ratio of expenditure to burden is the same for ASCVD as for NCDs. We note that NCDs encompass a range of diseases, including cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes (WHO, 2025), and that each of these are likely to have a different relationship between burden and expenditure. However, in the absence of ASCVD-specific estimates of this relationship, we assume the average relationship between burden and expenditure across all NCDs provides a *representative* estimate in this context.

4. As a final step, we weighted total healthcare expenditure by our adjusted ASCVD share of expenditure:

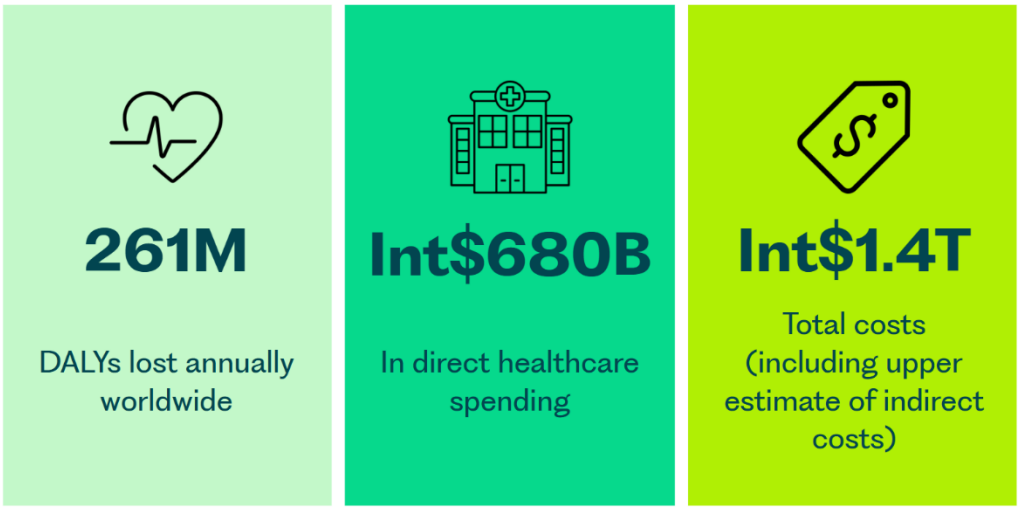
$$\begin{aligned} &ASCVD\ expenditure \\ &\quad \cong Total\ Health\ Expenditure \\ &\quad \times Adjusted\ ASCVD\ Exp.Share \end{aligned}$$

On the basis of this approach, we estimated that ASCVD is responsible for 261 million DALYs and Int$680 billion in direct healthcare spending around the world each year. Here, direct healthcare spending refers to healthcare spending from any financing source, be it public or private. For context, this figure is roughly the annual GDP of Sweden or Argentina (IMF, 2025).

This figure is an approximation, based on a number of assumptions required to overcome data gaps and differences in how countries around the world measure or report cost and burden, and therefore should be interpreted with some caution (our assumptions are described in greater detail in this paper's Limitations section). To assess the face validity of this result, we plotted our estimated global ASCVD DALY and expenditure shares alongside country-level shares. As shown in Appendix I — Methodology: Global burden of ASCVD, we found that our global estimate lies within the country-level estimates, supporting the validity of this estimate. Future research, though, should seek to confirm this result based on a more bottom-up methodology.

We extended this approach to try to estimate indirect costs, but we note that indirect costs — especially in lower- and middle-income countries — can be particularly challenging to estimate and interpret, given that these countries can have more informal labour markets and very different values of time, and different impacts on informal economies can be difficult to quantify. However, as a rough approximation, we assumed the global relationship between direct and indirect costs was the same as that observed in our country-specific analyses (see Country-level analyses). On the basis of this approximation, the total direct and indirect costs of ASCVD could be as high as Int$1.4 trillion — approximately 0.7% of global GDP (World Bank, 2025). This estimate, though, must be interpreted cautiously given the likely differences between indirect costs in more and less developed countries.

Figure 2 The global burden of ASCVD



Our results suggest that the largest spenders on ASCVD in terms of direct healthcare costs are the US, China, and Russia. In 2023, the countries with the most DALYs attributable to ASCVD are China, India, and Russia — these results are largely reflective of population size. When considering the relative disease burden of ASCVD in Europe, ASCVD has the largest impact in Eastern European countries, contributing over one-fifth of the total disease burden in Belarus, Ukraine, and Bulgaria. Similarly, we found that ASCVD had the most significant burden per capita in Eastern Europe, with Ukraine, Belarus, and the Republic of Moldova having the most ASCVD-related DALYs per person.

4 The estimated global burden of ASCVD attributable to elevated LDL-C

To estimate the share of ASCVD burden that LDL-C contributes to, we applied GBD estimates of population-attributable fractions (PAFs) (Institute for Health Metrics and Evaluation, 2024). PAFs are a standard approach to estimating the share of the burden of diseases associated with modifiable risk factors (Xiong et al., 2024; Tang et al., 2025; Counil, 2021; Gabet et al., 2024) and have been used previously to estimate economic burdens associated with elevated LDL-C (Reitzinger, Reiss and Czypionka, 2024).

PAFs represent the proportion of a particular measure of disease burden, such as prevalent cases, DALYs, YLLs, YLDs, or deaths that can be attributed to a specific exposure or risk level. In a world where no one is exposed to a particular risk factor, a proportion of the disease burden would not exist (Counil, 2021). If, for instance, the PAF for a specific risk factor was 30% then in a world where no one is exposed to the risk factor, in theory, 30% of the burden associated with that disease would not exist.

Consistent with the interpretation of the PAF as independent from the specific measure of burden, we assume that attributable burdens are directly proportional. That is, a PAF of 30% applies equally to attributable cases, DALYs or costs. We recognise that some DALYs may be more or less costly than others (for example, an additional DALY due to immediate death will be less costly than a DALY due to a debilitating stroke requiring constant care). However, we see no reason to expect that the distribution of cost for DALYs from LDL-C related ASCVD will be meaningfully different from the distribution of cost for DALYs from, say, smoking-related ASCVD. On this basis, we believe our assumption of proportionality across attributable burdens is justified.

Note that this is not to say this risk factor alone is responsible for 30% of a disease's burden, given patients are likely to have multiple overlapping risk factors contributing to disease. For example, in the case of LDL-C, other risk factors like high systolic blood pressure may jointly contribute to the same cases and disease outcomes as LDL-C. Rather, it indicates that this risk factor has a causal role in 30% of burden and, had it been at the level associated with minimum risk, this burden would not exist. Use of 'LDL-C attributable' terminology within this report refers to this concept. Full methodological details describing how we utilised PAFs are included in the Appendix (see: Applying PAFs).

The GBD defines exposure to high LDL-C as any level above the theoretical minimum risk exposure level (TMREL), which is defined in the GBD 2023 as 0.9-1.4 mmol/L (34.8-54.1 mg/dL) (Hay et al., 2025; Mensah et al., 2023). On the basis of this TMREL, any LDL-C greater than 1.4 mmol/L (54.1 mg/dL) is associated with an elevated risk of ASCVD outcomes. This includes not just those with clinically high LDL-C, but those deemed to have clinically "optimal" and "near optimal" LDL-C (Pappan, Awosika and Rehman, 2025). As such, the PAFs and subsequent burden estimated based on this TMREL represent an upper-bound estimate of the burden of LDL-C, and it is an over-estimate of the reduction in burden that could realistically be achieved.

We limited our analysis to the major clinical manifestations of ASCVD: IHD, IS, and PAD (Herrington et al., 2016), which is consistent with other literature quantifying the burden of ASCVD (Ji et al., 2025; Li et al., 2024; Nedkoff et al., 2023).

PAFs are estimated as an increasing function of the proportion of a population exposed to a certain risk factor—in this case, the proportion with LDL-C above the TMREL—and the relative risk of a disease outcome given exposure. The GBD PAFs show that high LDL-C

has one of the largest PAFs for included ASCVDs (Institute for Health Metrics and Evaluation, 2024; Hou et al., 2024).

We subsequently utilise PAFs reflecting the share of burden attributable to LDL-C to estimate the share of costs attributable to LDL-C. This approach implicitly assumes that the share of ASCVD burden attributable is a proxy for the share of ASCVD healthcare costs attributable to LDL-C, and has been adopted in previous cost-of-illness studies for modifiable risk factors (Saito et al., 2023; Xiong et al., 2024; Boachie et al., 2022). It also requires the assumption that an ASCVD DALY attributable to LDL-C cost the same as an ASCVD DALY attributable to another risk factor.

Applying the PAFs to the respective ASCVD-sub-diseases and their costs and burden in each country, we find that elevated LDL-C contributes to approximately Int$230 billion of the Int$680 billion in healthcare costs associated with ASCVD, approximately one third of the total. This result should be considered in the context of the limitations associated with the PAF methodology. **Though consistently used in academic literature, PAFs represent a theoretical maximum reduction that assumes complete elimination of the risk associated with elevated LDL-C in the population—a result that is not realistically achievable**. Still, these values are indicative of the upper bound of the avoidable burden of ASCVD and provide insight into the relative importance of LDL-C as a modifiable risk factor for ASCVD.

When considering indirect costs — assuming that the relationship between direct and indirect costs are the same in our country-specific analyses and the rest of the world — LDL-C contributes to Int$480 billion in total, or roughly the GDP of Vietnam (IMF, 2025). A proportion of this could be avoided through better detection and control of elevated LDL-C (Wilkinson, Lepor and Michos, 2023).. Again, though, this estimate is an approximation based on a number of assumptions and should be interpreted with caution.

Areas with the highest LDL-C associated burden included countries in the Gulf region, such as Kuwait, Qatar, and the United Arab Emirates.

This analysis took an implicit "counterfactual" approach (European Commission Joint Research Centre, 2026; UK Regulatory Policy Committee, 2020) to understanding the health and economic burdens associated with LDL-C related ASCVD. We implicitly compared health and economic outcomes under the *status quo* (i.e. the current burdens associated with elevated LDL-C nationally and globally) with a *hypothetical* counterfactual "state of the world" in which there are no ASCVD burdens related to LDL-C. The difference between these two scenarios represents the health and economic burdens associated with LDL-C related ASCVD, and by extension, the burden of LDL-C that is theoretically avoidable. In reality, achieving population-wide TMREL is not realistic, as clinicians target levels of LDL-C above the TMREL for much of the population (Pappan, Awosika and Rehman, 2025). This approach therefore represents a *hypothetical maximum.* Moreover, it does not evaluate specific strategies for reducing LDL-C as a risk factor. Reducing the burden will require some combination of primary and secondary prevention through early detection and effective management (World Health Organization, 2025b; Fragala, Shiffman and Birse, 2019; Thomas et al., 2023), but we do not account here for the relative effectiveness or the costs of different detection or management strategies.

In the next section, we look at a subset of countries with more detailed data on ASCVD burdens.

5 Country-level analyses

Our estimate of the scale of global burden of ASCVD and the LDL-related share is indicative, but it relies on a number of assumptions to overcome data limitations. Therefore, to supplement this global analysis, and to develop more granular estimates of burden and the share of potentially avoidable LDL-related burdens, we conducted a series of country-level analyses where more detailed country-specific data sources were available. We took a societal perspective, including both direct and indirect costs associated with ASCVD.

We developed estimates for nine countries around the world: the US, Canada, UK, Netherlands, France, Germany, Spain, Italy, and Japan. For each country, we followed the same three-step approach:

1. Using the GBD, we extracted the prevalence and LDL-C related PAFs for the key manifestations of ASCVD (IHD, IS, PAD, and polyvascular disease, which captures any combination of IHD, IS, and PAD (Smolderen et al., 2010).

2. We conducted a targeted literature review to identify country-specific estimates of the per-patient direct and indirect costs associated with each manifestation. We scaled these per-patient unit costs by the prevalence estimates collected in step 1.

3. We applied the country-specific PAFs on a disease-by-disease basis to estimate the overall burden of LDL-C.

Direct costs refer to health care expenditure from any financing source on areas such as primary care, outpatient care, emergency department attendances, inpatient hospital care, and medications. Indirect costs refer to productivity losses due to premature mortality, as well as productivity losses due to morbidity. In our analysis, morbidity specifically impacts absenteeism—taking sick days; presenteeism—working at a reduced capacity due to illness; and premature retirement. Finally, we include the cost of informal care to reflect the economic value of the unpaid care activities provided to individuals with ASCVD by friends and family members.

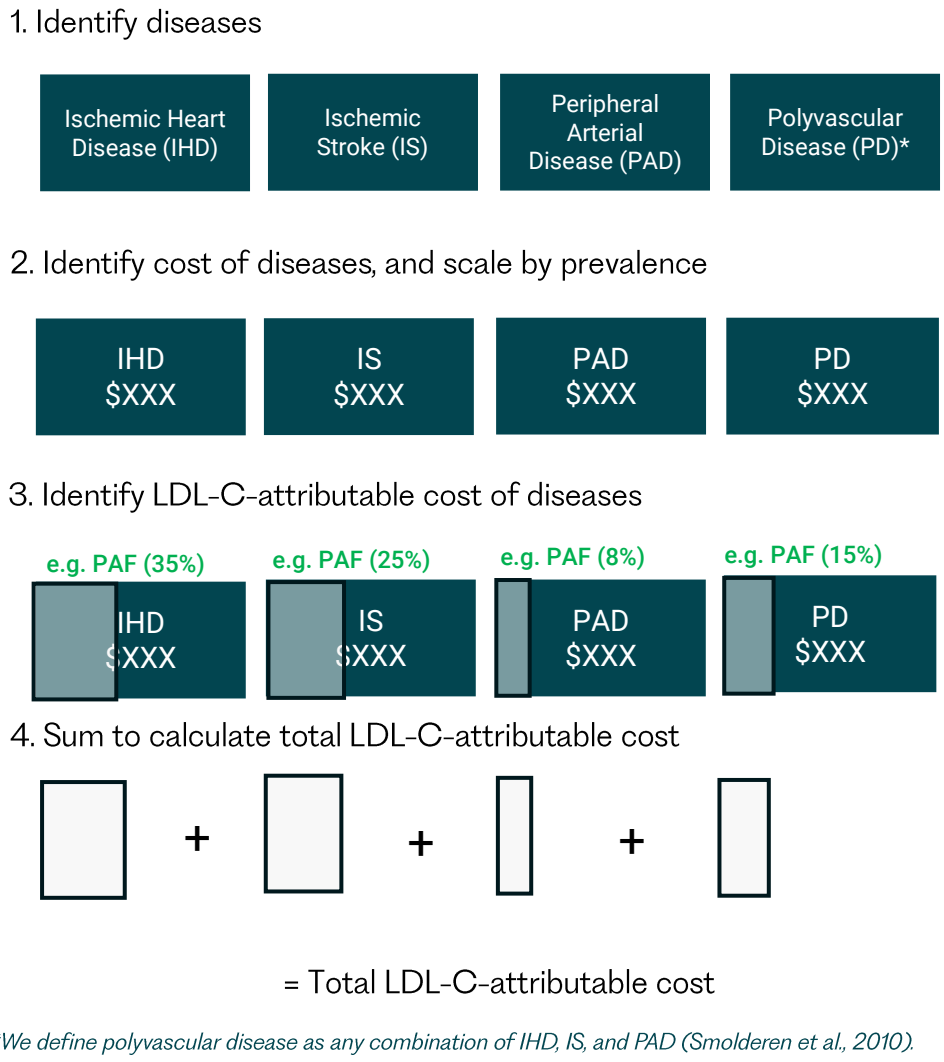
We do not include transfers such as pensions or other government payments in our analysis given our societal perspective, where money is moved from one party to another. This contrasts with spending on healthcare, which is a *cost*, because an hour of a healthcare provider's time spent on a ASCVD patient is an hour that cannot be spent on other types of healthcare. These transfers are important considerations when taking a treasury perspective.

PPP-adjusted international dollars (Int$) were used for cross-country aggregation to ensure comparability of real resource use in the global analysis, while nominal US dollars (US$) were used for country-specific estimates to reflect actual expenditures and facilitate interpretation by national stakeholders.

We also calculated the proportion of the LDL-C burden that is attributable to specific LDL-C levels in the UK to illustrate the relative contribution of different groups to the overall burden.

These steps are illustrated in Figure 3 below, and more methodological detail for each step, including our data sources, is available in Appendix 2 — Methodology: Country-level analyses.

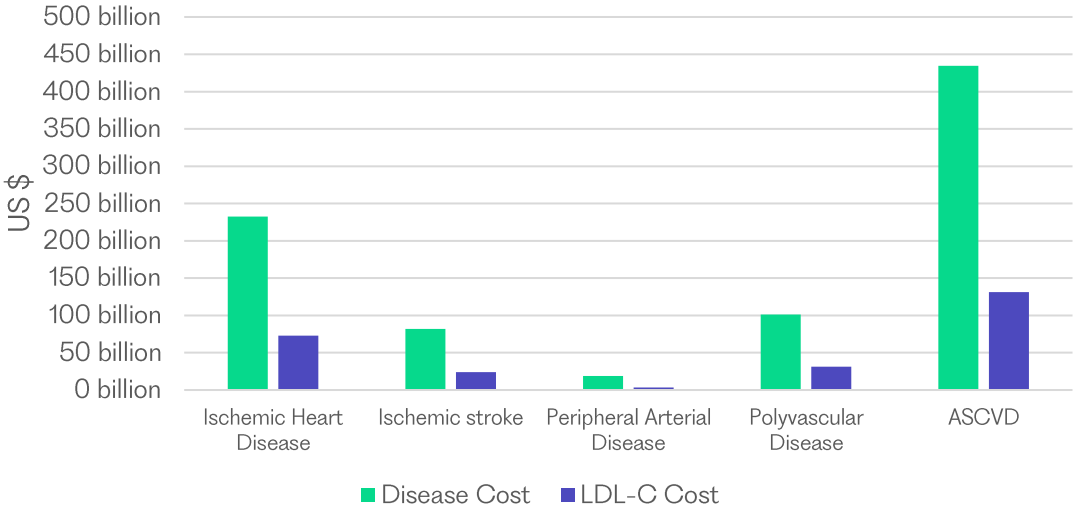
Figure 3 Methodological schematic



**We define polyvascular disease as any combination of IHD, IS, and PAD (Smolderen et al., 2010).*

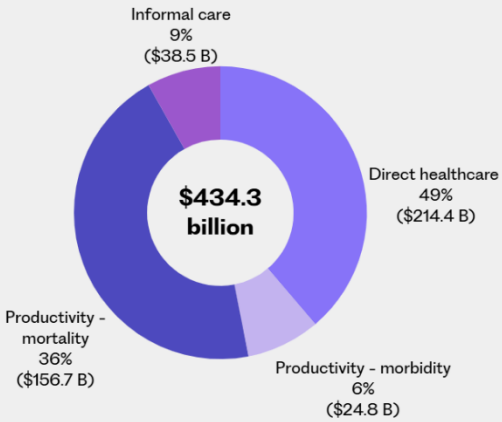
5.1 United States of America

Figure A1: Overall and LDL-C-attributable cost of ASCVDs in the US



The annual direct healthcare costs of ASCVD in the US are equivalent to US$214.4 billion in 2024 prices, which makes up 5.9% of US healthcare expenditure. Indirect costs are made up of productivity costs due to mortality and morbidity, as well as informal care costs (see Figure A2), and total US$219.9 billion. This amounts to an **overall cost to the economy of US$434.3 billion—2.3% of US GDP** (World Bank, 2024)—which is also equivalent to US$1297 per capita.

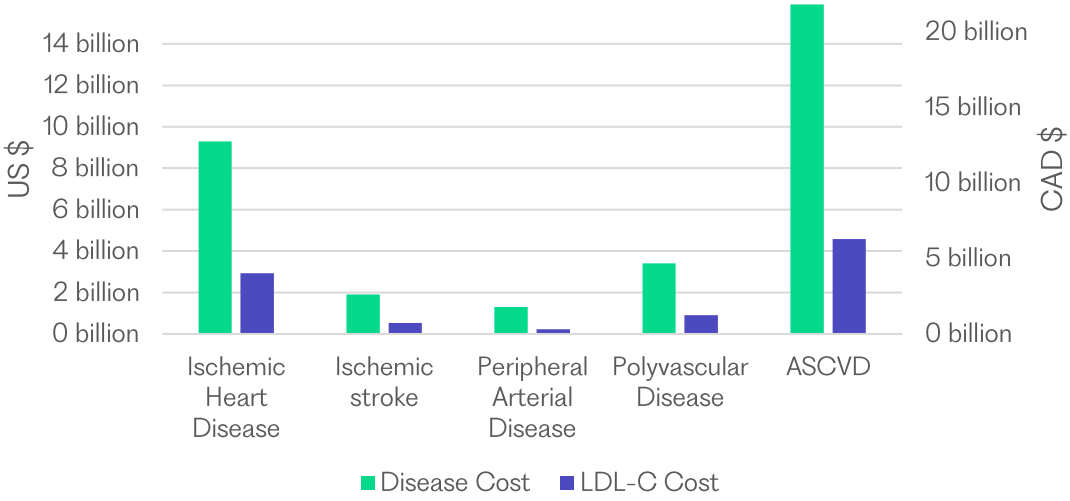
Figure A2: Contribution to total cost of ASCVD by component



US$131.4 billion of these costs may be attributed to elevated LDL-C, equating to US$392 per American citizen. This reflects the total economic burden of LDL-C related ASCVD, much of which could, in theory, be avoided if the whole population had LDL-C levels associated with no increased risk of disease outcomes. This estimate does not account for any future, unrelated health conditions.

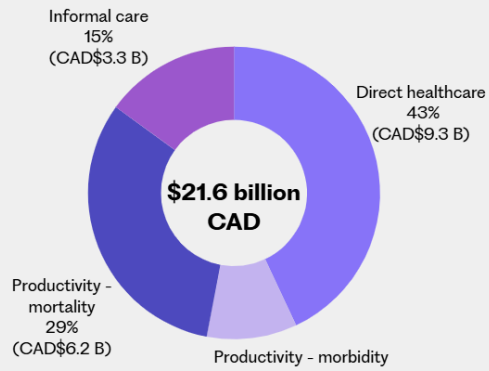
5.2 Canada

Figure B1: Overall and LDL-C-attributable cost of ASCVDs in Canada



The annual direct healthcare costs of ASCVD in Canada are equivalent to US$6.8 billion ($9.3 billion CAD) in 2024 prices, which makes up 3.7% of Canadian healthcare expenditure. Indirect costs are made up of productivity costs due to mortality and morbidity, as well as informal care costs (see Figure B2), and total US$9.0 billion ($12.3 billion CAD). This amounts to an **overall cost to the economy of US$15.8 billion ($21.6 billion CAD)—0.7% of Canadian GDP** (World Bank, 2024)—which is also equivalent to US$393 ($538 CAD) per capita.

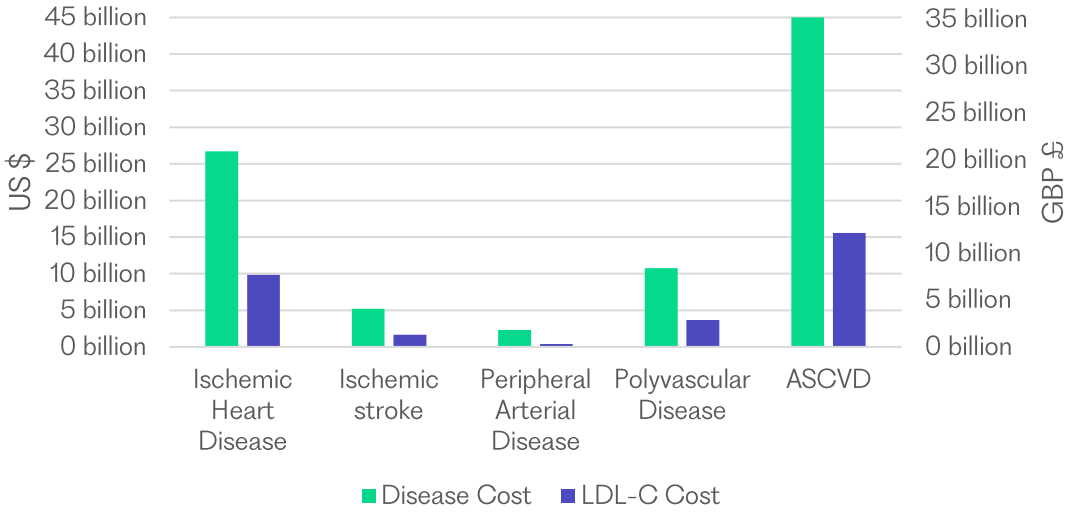
Figure B2: Contribution to total cost of ASCVD by component



US$4.6 billion ($6.3 billion CAD) of these costs may be attributed to elevated LDL-C, equating to US$114 ($157 CAD) per Canadian citizen. This reflects the total economic burden of LDL-C related ASCVD, much of which could, in theory, be avoided if the whole population had LDL-C levels associated with no increased risk of disease outcomes. This estimate does not account for any future, unrelated health conditions.

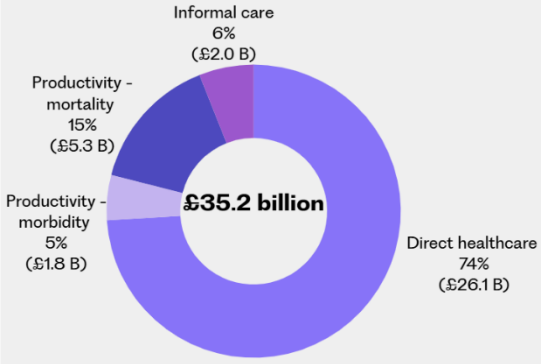
5.3 United Kingdom

Figure C1: Overall and LDL-C-attributable cost of ASCVDs in the UK



The annual direct healthcare costs of ASCVD in the UK are equivalent to US$33.4 billion (£26.1 billion) in 2024 prices, which makes up 11.5% of UK healthcare expenditure. Indirect costs are made up of productivity costs due to mortality and morbidity, as well as informal care costs (see Figure C2), and total US$11.6 billion (£9.1 billion). This amounts to an **overall cost to the economy of US$45.0 billion (£35.2 billion)—1.2% of UK GDP** (World Bank, 2024)—which is also equivalent to US$658 (£515) per capita.

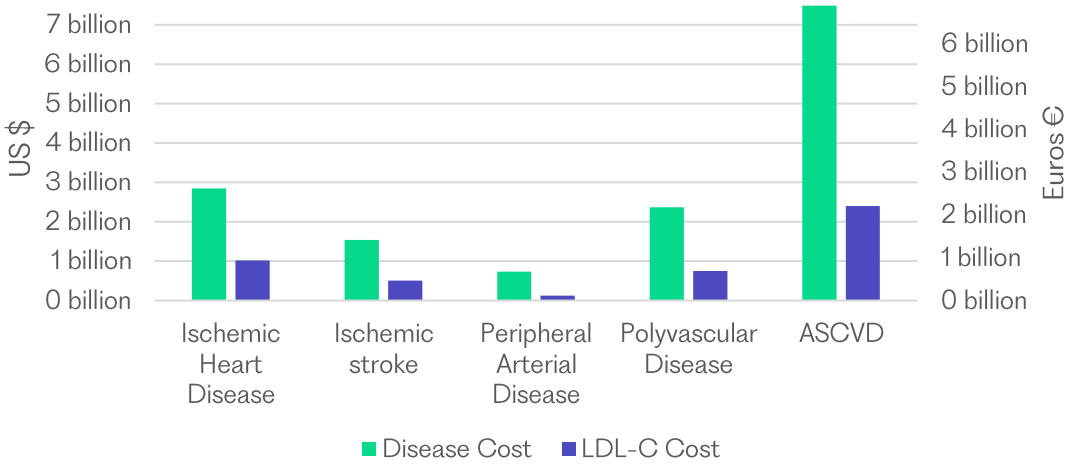
Figure C2: Contribution to total cost of ASCVD by component



US$15.6 billion (£12.2 billion) of these costs may be attributed to elevated LDL-C, equating to US$228 (£178) per UK citizen. This reflects the total economic burden of LDL-C related ASCVD, much of which could, in theory, be avoided if the whole population had LDL-C levels associated with no increased risk of disease outcomes. This estimate does not account for any future, unrelated health conditions.

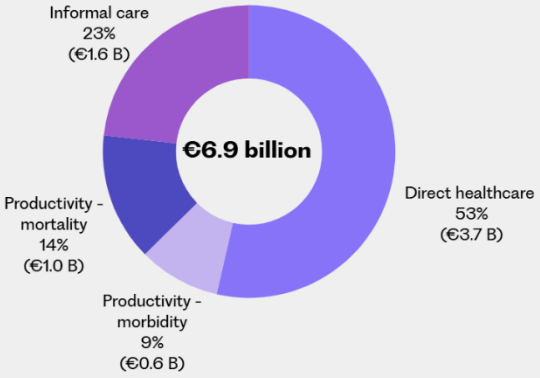
5.4 Netherlands

Figure D1: Overall and LDL-C-attributable cost of ASCVDs in the Netherlands



The annual direct healthcare costs of ASCVD in Netherlands are equivalent to US$4.0 billion (€3.7 billion) in 2024 prices, which makes up 5.3% of Dutch healthcare expenditure. Indirect costs are made up of productivity costs due to mortality and morbidity, as well as informal care costs (see Figure D2), and total US$3.5 billion (€3.3 billion). This amounts to an **overall cost to the economy of US$7.5 billion (€6.9 billion)—0.6% of the Netherlands' GDP** (World Bank, 2024)—which is also equivalent to US$419 (€387) per capita.

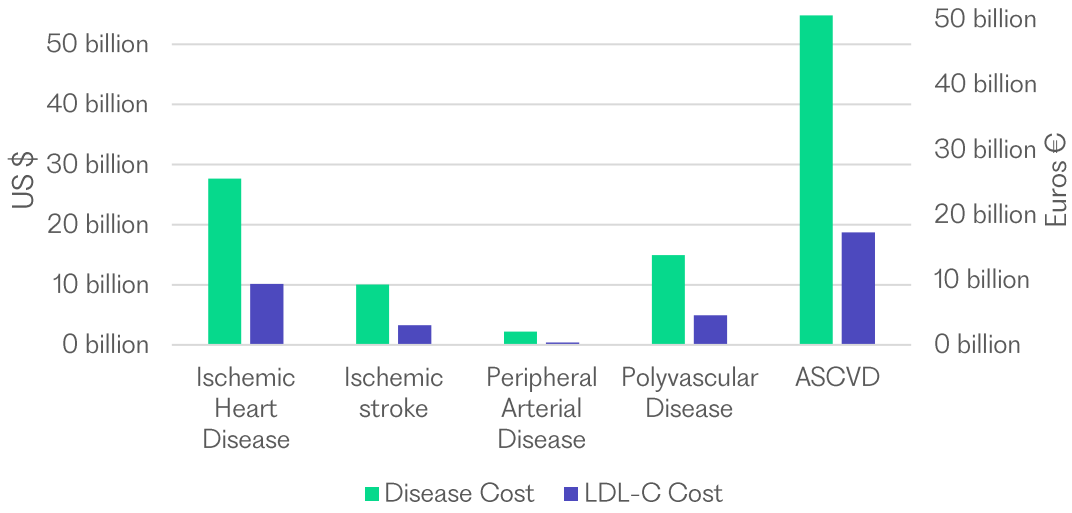
Figure D2: Contribution to total cost of ASCVD by component



US$2.4 billion (€2.2 billion) of these costs may be attributed to elevated LDL-C, equating to US$134 (€124) per Dutch citizen. This reflects the total economic burden of LDL-C related ASCVD, much of which could, in theory, be avoided if the whole population had LDL-C levels associated with no increased risk of disease outcomes. This estimate does not account for any future, unrelated health conditions.

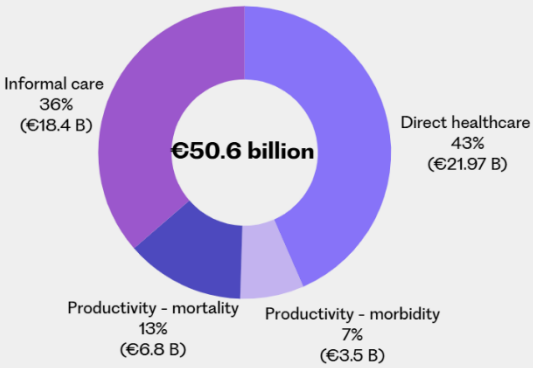
5.5 Germany

Figure E1: Overall and LDL-C-attributable cost of ASCVDs in Germany



The annual direct healthcare costs of ASCVD in Germany are equivalent to US$23.7 billion (€21.9 billion) in 2024 prices, which makes up 6.1% of German healthcare expenditure. Indirect costs are made up of productivity costs due to mortality and morbidity, as well as informal care costs (see Figure E2), and total US$31.1 billion (€28.7 billion). This amounts to an **overall cost to the economy of US$54.8 billion (€50.6 billion)—1.2% of German GDP (World Bank, 2024)**—which is also equivalent to US$658 (€608) per capita.

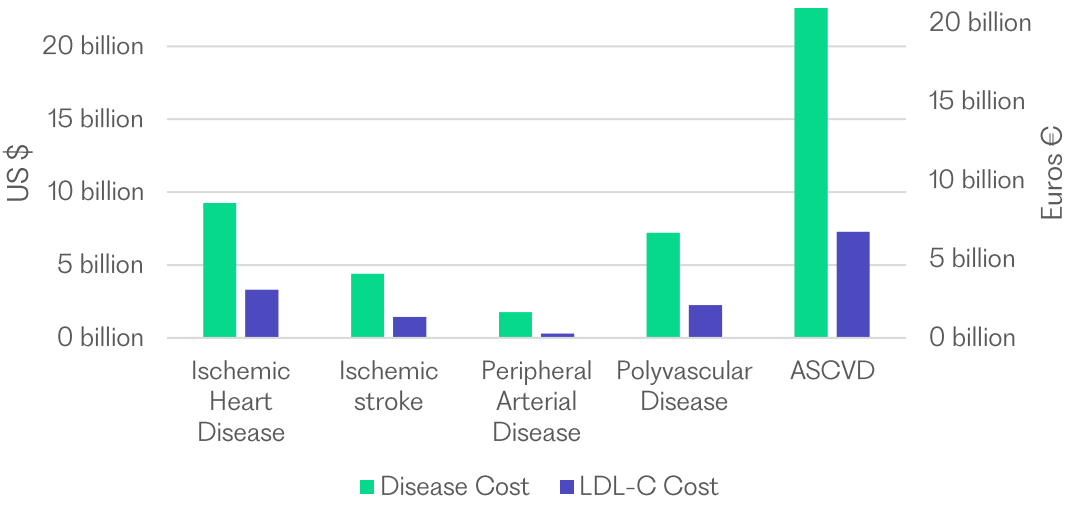
Figure E2: Contribution to total cost of ASCVD by component



US$18.7 billion (€17.3 billion) of these costs may be attributed to elevated LDL-C, equating to US$225 (€208) per German citizen. This reflects the total economic burden of LDL-C related ASCVD, much of which could, in theory, be avoided if the whole population had LDL-C levels associated with no increased risk of disease outcomes. This estimate does not account for any future, unrelated health conditions.

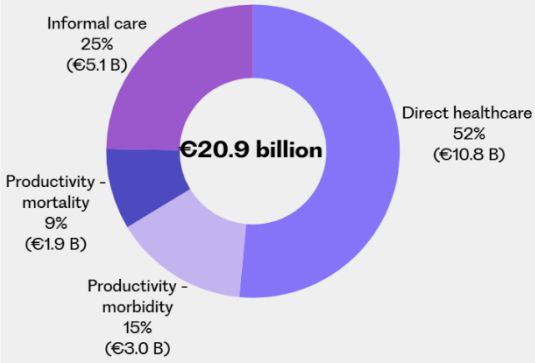
5.6 France

Figure F1: Overall and LDL-C-attributable cost of ASCVDs in France



The annual direct healthcare costs of ASCVD in France are equivalent to US$11.7 billion (€10.8 billion) in 2024 prices, which makes up 4.3% of French healthcare expenditure. Indirect costs are made up of productivity costs due to mortality and morbidity, as well as informal care costs (see Figure F2), and total US$10.9 billion (€10.1 billion). This amounts to an **overall cost to the economy of US$22.6 billion (€20.9 billion)—0.7% of France's GDP (World Bank, 2024)**—which is also equivalent to US$331 (€306) per capita.

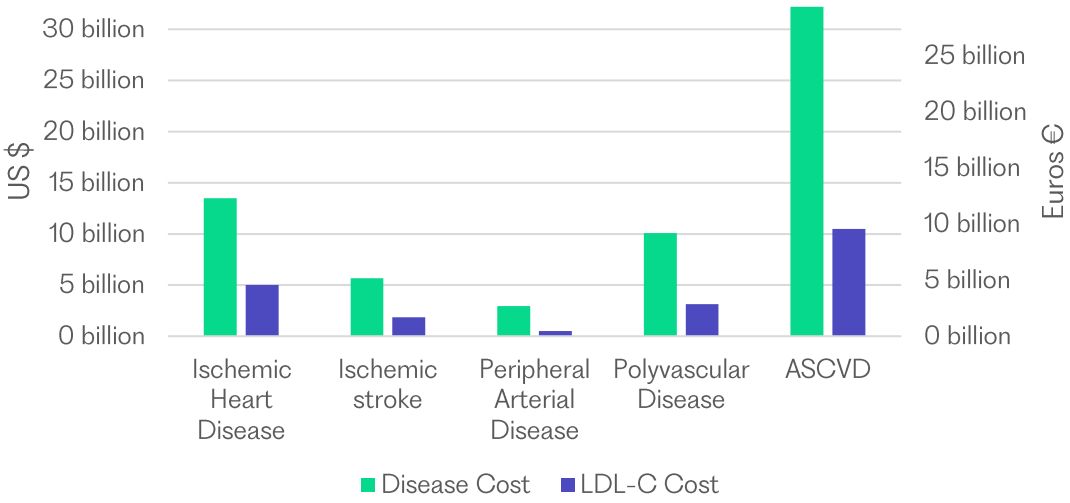
Figure F2: Contribution to total cost of ASCVD by component



US$7.3 billion (€6.7 billion) of these costs may be attributed to elevated LDL-C, equating to US$106 (€98) per French citizen. This reflects the total economic burden of LDL-C related ASCVD, much of which could, in theory, be avoided if the whole population had LDL-C levels associated with no increased risk of disease outcomes..This estimate does not account for any future, unrelated health conditions.

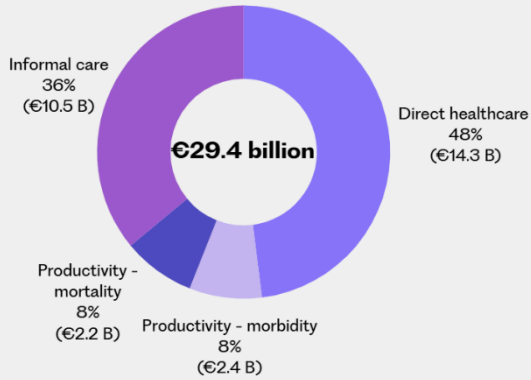
5.7 Italy

Figure G1: Overall and LDL-C-attributable cost of ASCVDs in Italy



The annual direct healthcare costs of ASCVD in Italy are equivalent to US$15.8 billion (€14.3 billion) in 2024 prices, which makes up 9.5% of Italian healthcare expenditure. Indirect costs are made up of productivity costs due to mortality and morbidity, as well as informal care costs (see Figure G2), and total US$16.4 billion (€15.1 billion). This amounts to an **overall cost to the economy of US$32.2 billion (€29.4 billion)—1.4% of Italy's GDP** (World Bank, 2024)—which is also equivalent to US$546 (€498) per capita.

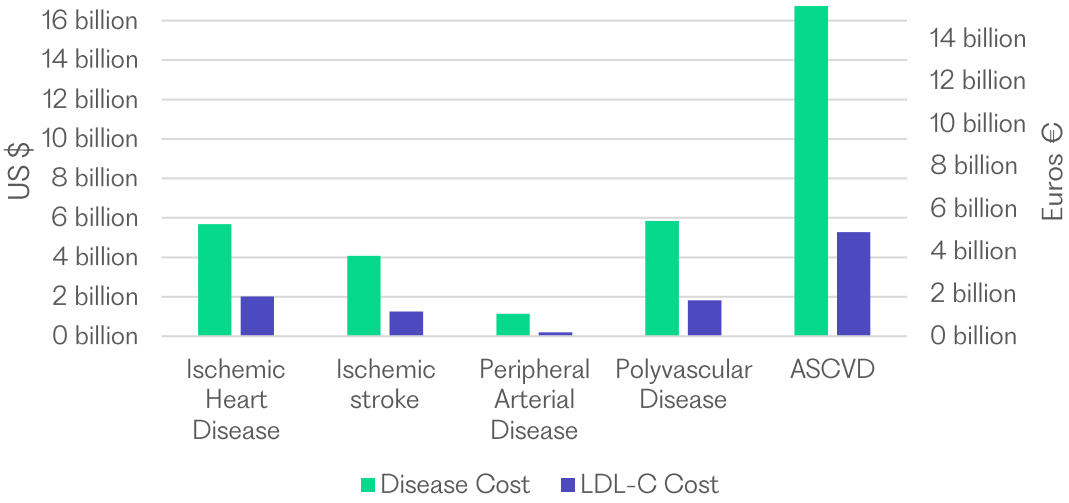
Figure G2: Contribution to total cost of ASCVD by component



US$10.5 billion (€9.6 billion) of these costs may be attributed to elevated LDL-C, equating to US$178 (€163) per Italian citizen. This reflects the total economic burden of LDL-C related ASCVD, much of which could, in theory, be avoided if the whole population had LDL-C levels associated with no increased risk of disease outcomes. This estimate does not account for any future, unrelated health conditions.

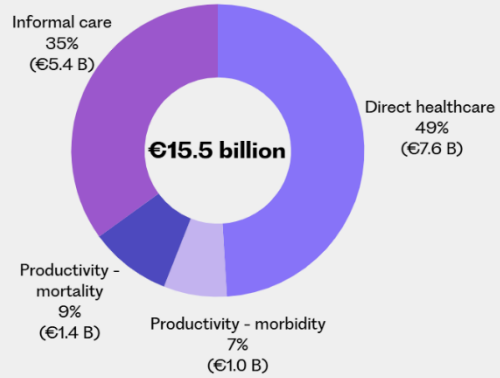
5.8 Spain

Figure H1: Overall and LDL-C-attributable cost of ASCVDs in Spain



The annual direct healthcare costs of ASCVD in Spain are equivalent to US$8.2 billion (€7.6 billion) in 2024 prices, which makes up 6.3% of Spanish healthcare expenditure. Indirect costs are made up of productivity costs due to mortality and morbidity, as well as informal care costs (see Figure H2), and total US$8.5 billion (€7.9 billion). This amounts to an **overall cost to the economy of US$16.7 billion (€15.5 billion)—1.0% of Spain's GDP** (World Bank, 2024)—which is also equivalent to US$346 (€320) per capita.

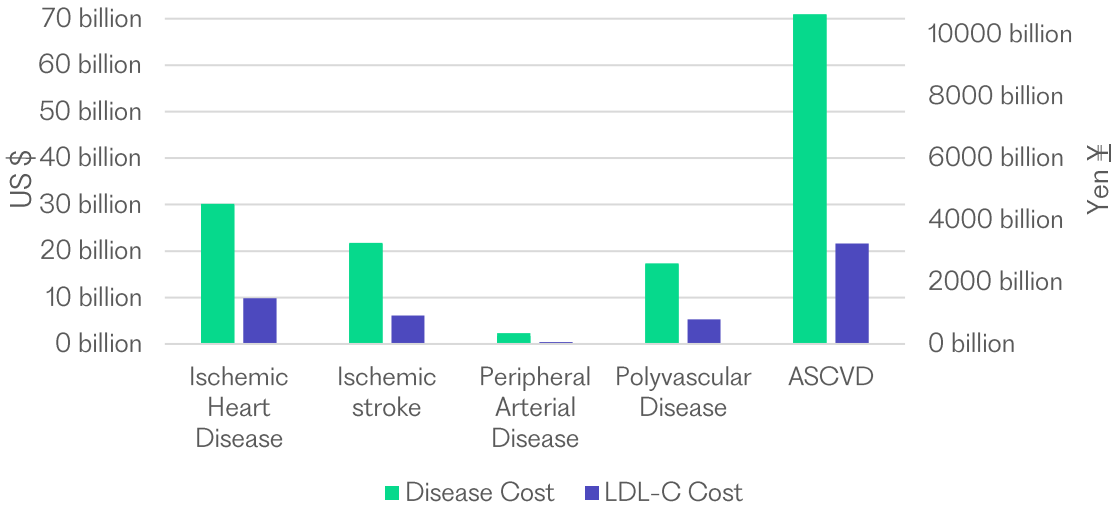
Figure H2: Contribution to total cost of ASCVD by component



US$5.3 billion (€4.9 billion) of these costs may be attributed to elevated LDL-C, equating to US$109 (€101) per Spanish citizen. This reflects the total economic burden of LDL-C related ASCVD, much of which could, in theory, be avoided if the whole population had LDL-C levels associated with no increased risk of disease outcomes. This estimate does not account for any future, unrelated health conditions.

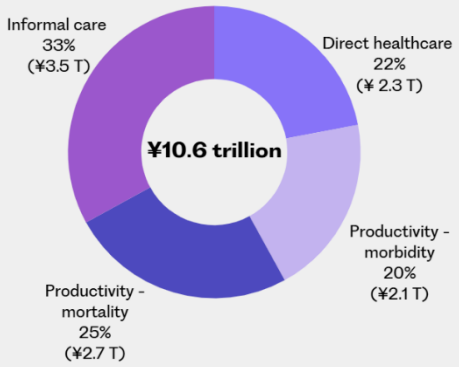
5.9 Japan

Figure I1: Overall and LDL-C-attributable cost of ASCVDs in Japan



The annual direct healthcare costs of ASCVD in Japan are equivalent to US$15.8 billion (¥2,298.0 billion) in 2024 prices, which makes up 4.0% of Japanese healthcare expenditure.. Indirect costs are made up of productivity costs due to mortality and morbidity, as well as informal care costs (see Figure I2), and total US$55.1 billion (¥8,341.8 billion). This amounts to an **overall cost to the economy of US$70.9 billion (**¥10,639.8 billion)—**1.8% of Japan's GDP (World Bank, 2024)**—which is equivalent to US$570 (¥85,449) per capita.

Figure I2: Contribution to total cost of ASCVD by component



US$21.6 billion (¥3,252.0 billion) of these costs may be attributed to elevated LDL-C, equating to US$173 (¥26,117) per Japanese citizen. This reflects the total economic burden of LDL-C related ASCVD, much of which could, in theory, be avoided if the whole population had LDL-C levels associated with no increased risk of disease outcomes. This estimate does not account for any future, unrelated health conditions.

5.10 Summary of health and economic burden by country

We summarise our country-level analyses in Table 1 below, which shows that the country with the most substantial per-patient losses due to ASCVD is the US, which is unsurprising given the US's health expenditure and value of time. Behind the US are the UK and the Netherlands, where patients cost close to US$10,000 per year. In absolute terms, ASCVD imposes the largest burden on the United States, Japan, and Germany.

Table 1 Summary of ASCVD cost components across countries

	United States	Canada	United Kingdom	Netherlands	Germany	France	Italy	Spain	Japan
DIRECT COSTS (US$ BN)	214.4	6.8	33.4	4.0	23.7	11.7	15.8	8.2	15.8
PRODUCTIVITY LOSSES — MORBIDITY (US$ BN)	24.8	2.0	2.3	0.7	3.8	3.3	2.6	1.1	14.1
PRODUCTIVITY LOSSES — MORTALITY (US$ BN)	156.7	4.5	6.7	1.1	7.4	2.1	2.4	1.5	17.6
INFORMAL CARE COSTS (US$ BN)	38.5	2.4	2.6	1.7	19.9	5.5	11.4	5.9	23.4
TOTAL INDIRECT COSTS (US$ BN)	219.9	9.0	11.6	3.5	31.1	10.9	16.4	8.5	55.1
TOTAL ASCVD COSTS (US$ BN)	434.3	15.8	45.0	7.5	54.8	22.6	32.2	16.7	70.9
LDL-C ATTRIBUTABLE COST (US$ BN)	131.4	4.6	15.6	2.4	18.7	7.3	10.5	5.3	21.6
ASCVD COST PER PATIENT (US$ THOUSANDS)	17.9	5.4	10.8	9.5	7.1	6.4	8.3	7.6	7.5
LDL-C ATTRIBUTABLE COST PER PATIENT (US$ THOUSANDS)	5.4	1.6	3.8	3.0	2.4	2.1	2.7	2.4	2.3

Note that this table is meant only to summarise the results of our analyses. Any comparisons between countries should be approached with caution due to different data sources and definitions of cost components.

Indirect costs are larger than direct costs in 6 out of the 9 countries studied, highlighting the impact of ASCVD beyond the health system. In most cases, the primary driver of indirect costs are the productivity losses due to mortality. Also significant are the informal care costs—an often-overlooked contributor to disease burden—with productivity losses among caregivers comparable to the productivity losses associated with mortality and morbidity in ASCVD patients.

Additionally, Table 1 shows that the LDL-C-attributable costs amount to approximately one-third of the total costs of ASCVD. In per-patient terms, elevated LDL-C contributes between US$1.6 thousand and US$5.4 thousand per patient per year. Considering that elevated LDL-C is preventable, these figures can be understood as highlighting that up to a third of all costs owed to ASCVD could theoretically be avoided through controlled LDL-C across these countries. We note that any comparisons should be approached with caution, due to the differing data sources and definitions of cost components across countries.

Table 2 Health burden of ASCVD by country

	ASCVD DALYs	ASCVD DALYs PER PATIENT	ASCVD YLLs	ASCVD YLLs PER PATIENT	ASCVD MORTALITY	TOTAL PATIENTS	POPULATION
UNITED STATES	11,765,583	0.485	10,091,554	0.416	601,576	24,239,100	335,414,198
CANADA	1,059,003	0.362	875,186	0.299	58,358	2,923,878	38,402,385
UNITED KINGDOM	2,103,364	0.507	1,852,249	0.446	120,619	4,148,422	69,165,653
NETHERLANDS	384,223	0.487	372,218	0.415	23,681	789,138	17,783,978
GERMANY	3,628,176	0.473	3,095,064	0.403	220,585	7,676,520	84,444,278
FRANCE	1,385,839	0.393	1,126,275	0.319	82,005	3,530,247	69,873,339
ITALY	1,763,796	0.454	1,524,829	0.393	120,096	3,878,408	58,894,072
SPAIN	1,065,600	0.483	895,593	0.406	63,313	2,206,263	47,678,556
JAPAN	3,684,824	0.392	2,963,286	0.315	231,571	9,397,942	124,672,697

In Table 2, we present the health burden of ASCVD, as represented by DALYs, YLLs, and mortality. We also provide each country's population size to contextualise these results (Institute for Health Metrics and Evaluation, 2024). Consistent with the overall cost burdens, ASCVD imposes the largest health burden on the US in both absolute and per-patient terms, where it accounts for 0.485 DALYs per patient. Per patient DALYs are similar in the UK, Netherlands, Germany, Spain, and Italy, where ASCVD is responsible for roughly 0.5 DALYs per patient.

6 Calculating the burden of LDL-C at different thresholds

Our estimates of the burden linked to LDL-C are, unavoidably, a function of the threshold used to define 'elevated'. A higher threshold for 'elevated' will produce a relatively lower estimate of burden, whereas a lower (i.e. more inclusive) threshold will produce a higher estimate of burden. As such, it is useful to understand how burden changes with changes in the threshold for elevated LDL-C, and how different LDL-C targets affect the overall burden.

The PAFs used in the previous sections were used to calculate the *total burden* of any elevated LDL-C i.e. any LDL-C above TMREL. However, to estimate the contribution of different LDL-C levels (or categories) to the overall burden, we must estimate LDL-C level-specific PAFs. These level-specific PAFs are—like the overall PAFs—a function of relative risk (RR) and prevalence; that is, a higher level-specific PAF might be due to a larger proportion of the population having that level of LDL-C, or that level corresponding to a higher risk of a disease outcome (such as death or disability).

Each country and each disease in our analysis has its own PAF, calculated by the Global Burden of Disease (Hay et al., 2025), based on the prevalence of elevated LDL-C as a risk factor, and the relative risk of different ASCVD sub-diseases given elevated LDL-C. Within this overall attributable fraction, the burden — such as cases, DALYs, or costs — can be further broken down by LDL-C category, such as the ranges in Table 3 on the next page.

To calculate these range-specific contributions for the UK as a case study, we utilised the PAF equation below to calculate the LDL-C level-specific PAFs. Further details are included in Appendix 2 — Methodology: Country-level analyses.

$$\text{PAF} = \frac{\text{p}(\text{RR} - 1)}{\text{p}(\text{RR} - 1) + 1}$$

where p = prevalence of exposure and RR = relative risk of disease outcome associated with exposure to the risk factor.

6.1 LDL-C category analysis: United Kingdom

In this section, we describe how the economic burden of LDL-C changes according to the LDL-C concentration being considered, using the UK as a case study.

The economic burden attributable to different LDL-C risk categories in the United Kingdom is shown in Table 3. While optimal LDL-C levels are influenced by factors such as age, sex, and cardiovascular disease history, the ranges provided in Table 3 are accepted as generally reflective of risk profiles across different LDL-C levels (Pappan, Awosika and Rehman, 2025).

Table 3 Economic burden of ASCVDs attributable to LDL-C categories in the UK

Figures based on OHE calculations.
IHD=Ischemic Heart Disease; IS=Ischemic Stroke; PAD=Peripheral arterial disease.

** The British Heart Foundation considers <3.0 mmol/L (116.0 mg/dL) to be a healthy level of LDL-C (British Heart Foundation, 2024).*

LDL-C CATEGORY	ECONOMIC BURDEN (US$ millions)			
	IHD	IS	PAD	COMBINED (%)
Optimal* <2.6 mmol/L <100.5 mg/dL	825	139	33	997 (8%)
Near/above optimal 2.6–3.3 mmol/L 100.5–127.6 mg/dL	2,171	366	87	2,624 (22%)
Borderline high 3.4–4.1 mmol/L 127.6–158.6 mg/dL	2,930	493	117	3,540 (30%)
High 4.1–4.9 mmol/L 158.5–189.5 mg/dL	2,304	388	92	2,784 (23%)
Very high ≥ 4.9 mmol/L 189.5 mg/dL	1,590	268	64	1,922 (16%)
OVERALL	9,820	1,654	393	11,867 (100%)

Although the individual risk of ASCVD outcomes and associated per patient burdens increase with LDL-C, these results indicate — somewhat counterintuitively — that the overall economic burdens are greatest in the 'borderline high' range. This result is consistent with the "Prevention Paradox" described by Rose, Khaw and Marmot (2008): although *per patient* costs tend to increase with risk, it is the moderate risk groups that have the greatest *aggregate* burden. This is because there are typically more patients in the moderate risk groups than in the higher risk groups. For example, for IHD, we estimated that the borderline high risk group accounts for almost twice the economic burden of the very high risk group (US$2,930 million vs US$1,590 million), despite a lower probability of an ASCVD event.

Figure 4 shows the distribution of ASCVD prevalence by LDL-C level (black line) and the distribution of the total LDL-C-associated economic burden by ASCVD sub-disease and LDL-C level (purple bars). Both follow a similar 'bell curve' or inverted-U shape, even though total cost per case would be expected to be higher among patients with higher LDL-C. This reflects the fact that total cost is a function of both cost per case *and* the number cases at a particular LDL-C level. The greater number of cases in the moderate LDL-C range, even at a relatively lower cost per case, outweigh the higher cost per case among a smaller number of cases in the higher LDL-C range.

All costs in Table 3 and all cost bars in Figure 4 are calculated from our UK cost estimates, alongside relative risks derived from Ference et al. (2012) and prevalence estimates from IHME (Institute for Health Metrics and Evaluation, 2024).

Figure 4 Economic burden of ASCVDs attributable to LDL-C levels in the UK

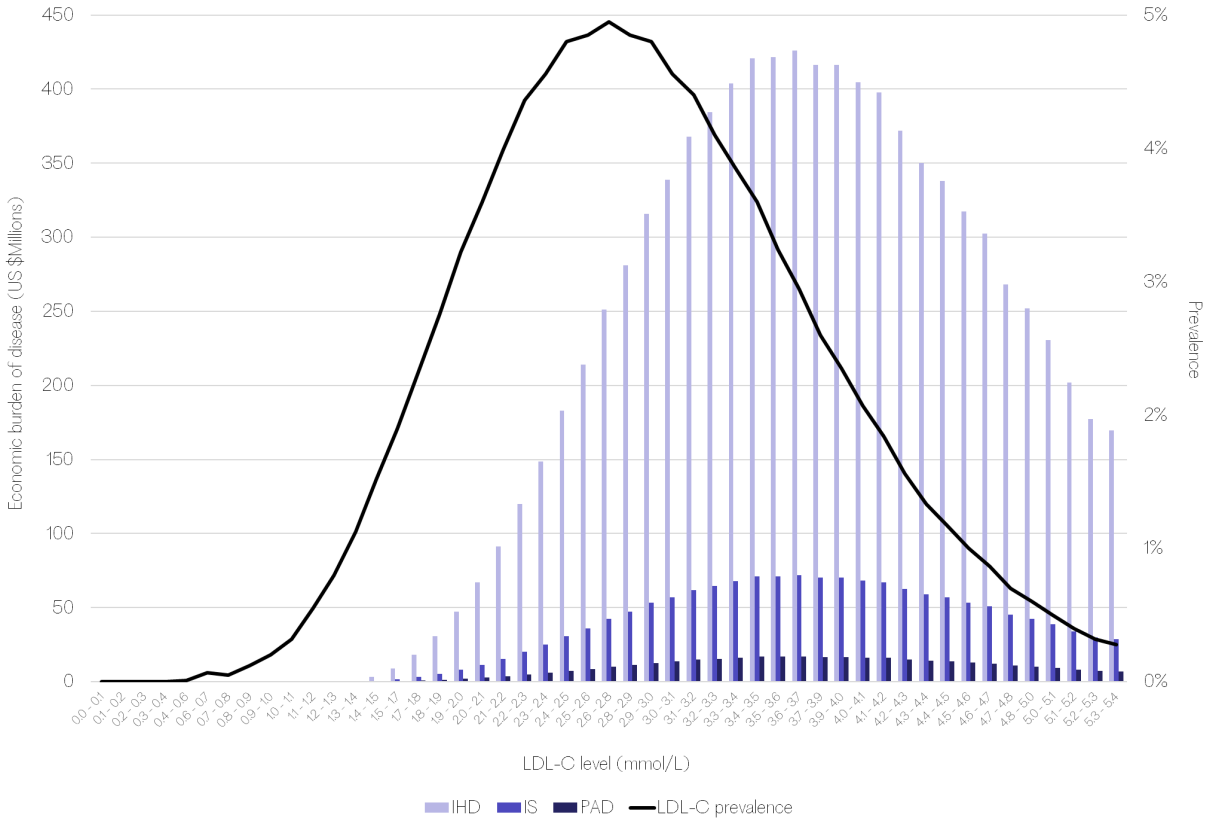


Figure is based on OHE calculations, with relative risks derived from Ference et al. (2012) and prevalence estimates from IHME (Institute for Health Metrics and Evaluation, 2024).

7 Discussion

We have demonstrated that ASCVD may cost the globe Int$680 billion in direct healthcare costs, of which elevated LDL-C contributes to approximately one-third. Additionally, our country-specific analyses have shown that ASCVD costs countries between $US5.4 thousand in Canada and US$17.9 thousand in the United States per patient per year.

Not highlighted in these results, however, are the effects borne by patients on a daily basis. Indeed, IHD, IS, and PAD and their major clinical events are characterised by significant health-related quality of life decrements. For instance, many stroke survivors are unable to work and, as a result, must receive financial assistance, as well as forms of caregiving from family members, who are often ill-equipped to fill such a role (Ramos-Lima et al., 2018). Likewise, people with symptomatic PAD can sometimes experience functional limitations so severe that they find their ability to participate in their daily activities restricted, and many patients also suffer from anxiety and depression due to fear of amputation and chronic progression of the disease (Abuhalimeh and Christopher, 2024).

In addition to its significant humanistic and socioeconomic burden, ASCVD is associated with health inequities that cannot easily be captured by quantitative figures. In the United States, for instance, ASCVD risk is much greater among those considered low income and among people with less than a college education (Tremblay et al., 2024). In terms of disease management, it is reported that statin utilization in the United States is lower among women compared to men, suggesting that there could be gender inequities in disease management of ASCVD (Shahid et al., 2024). Interventions aiming to reduce the prevalence and impact of ASCVD could, thus, consequently have the effect of addressing health equity concerns.

Still, our analysis has shown that the largest driver of direct spending on ASCVD is hospitalisations—when patients experience a major clinical event, often requiring emergency and/or critical care, pointing to significant headroom for spending on prevention. Indeed, additional spending on preventative care would have the effect of reducing ASCVD's total disease burden and the hospitalisations — and therefore costs — resulting from ASCVD.

Beyond its impact on direct costs on health losses, investing in prevention could likewise decrease the significant indirect costs that ASCVD imposes on society more broadly. Informal care costs are notable portion of these indirect costs — in some countries, costs associated with informal care exceed productivity costs for patients themselves.

Our UK-specific analysis highlighted that *borderline high* and *high* categories of LDL-C, contribute more to the overall disease burden than the *Very high* categories, due to the prevalence within these categories. Investment in LDL-C lowering therapies should therefore apply to patients across the LDL-C spectrum if maximum burden is to be avoided.

7.1 Priorities for intervention

A significant portion of the costs of ASCVD are preventable — our analysis demonstrated the avoidable burden associated with one preventable risk factor in particular, LDL-C, is substantial. For existing patients, therapies have the potential to reduce risk of ASCVD outcomes through lowering LDL-C, with subsequent reductions in economic burden. It is important to note that achieving lower levels of LDL-C in these patients would not

eliminate all burden due to cumulative risk of previous LDL-C exposure, which increases risk of ASCVD independent of current LDL-C level (Zhang et al., 2021).

Guidelines across the world recommend lowering LDL-C and increased intensity of interventions as risk of cardiovascular disease becomes higher (Mach et al., 2025; Grundy et al., 2019; Pearson et al., 2021). These guidelines are based on clinical trial evidence demonstrating the efficacy of these treatments at achieving lower LDL-C and improved treatment outcomes, highlighting their potential to reduce the avoidable burden of ASCVD in the real world. Recently, ESC guidelines for the targeting and treatment of LDL-C have become more stringent than in other regions, in light of increasing clinical trial evidence that 'lower is better', in particular the further benefit of lowering LDL-C to 70 mg/dL (1.8 mmol/L) in terms of cardiovascular outcomes (Aygun and Tokgozoglu, 2022). Targeting specific LDL-C levels rather than percentage reductions may generate additional clinical benefit (Kang et al., 2025). However, clinical studies have highlighted under-implementation of guidelines, under-utilisation of high-dose statins and combination therapies, and that only a third of patients in the Euroaspire V trial achieved their LDL-C goals. (Aygun and Tokgozoglu, 2022).

Lifestyle interventions, such as diet and exercise programmes, have been shown to reduce LDL-C levels by 10-15% in randomised studies (Wadhera et al., 2016). For example, the Mediterranean diet was shown to reduce LDL-C levels by 10% after 5 weeks, and randomised studies indicate physical activity leading to a decrease in small LDL particle number (Kraus et al., 2002; Richard et al., 2012). Moreover, diet and exercise combined is more effective than either approach alone (Varady and Jones, 2005).

However, such reductions are often insufficient to prevent further events in high-risk patients who have suffered a cardiac event (Amarenco et al., 2023). Additionally, the impact of diet and exercise interventions in practice can be limited due to adherences issues. One study exploring LDL-C target achievement in patients with type 2 diabetes found adherence to dietary components was particularly poor (Gant et al., 2018). Statin use and dosage was higher in patients who achieved LDL-C targets compared to those who did not, indicating pharmaceutical interventions are often necessary in addition to lifestyle interventions to achieve target LDL-C levels (Gant et al., 2018). As such, ESC guidelines encourage LLTs if any patient is above their target LDL-C, as judged by their cardiovascular risk level (Mach et al., 2025).

LLTs remain underutilised due to under prescribing or suboptimal dosing, leading to deficient control of LDL-C in patients. The SANTORNI study found the vast majority of high-risk and very high-risk patients failed to achieve 2019 ESC guideline recommendations, with a potential cause being underestimation of cardiovascular risk and subsequent suboptimal treatment intensity, such as low utilisation of combination therapies or higher-intensity LDL-C-lowering medications (Ray et al., 2023; Arca et al., 2018).

Moreover, among patients with high and very high CV risk, combination therapies have been shown to better control LDL-C levels than monotherapy (Ray et al., 2024)—indeed, for the vast majority of very high-risk patients, statin monotherapy alone will not be sufficient to achieve target LDL-C levels (Ray et al., 2023). Again, these therapies remain underutilised in clinical practice (Şener and Tokgözoğlu, 2023).

Given high LDL-C is often asymptomatic, screening is necessary to identify risk of more severe conditions. American guidelines recommend adults at low risk for cardiovascular disease (CVD) receive cholesterol screening at least every 4-6 years, and more frequent screenings are recommended for those with elevated risk for heart disease and stroke (Writing Committee Members et al., 2026). 42.7% of US adults with LDL-C levels between 160-189 mg/dL (4.1-4.9 mmol/L) were unaware and untreated, highlighting shortcomings in current screening coverage. This lack of awareness being more common in younger adults, men, and racial and ethnic minority groups (Sayed et al., 2023).

These insights, combined with the results from our analysis, suggest improving implementation of treatment guidelines could substantially reduce the avoidable burden due to LDL-C. Each health system should aim to understand the particular barriers that are preventing patients from achieving their LDL-C goals.

7.2 Limitations

The results of our global analysis should be interpreted in the context of several limitations. For one, we derive these estimates based on a combination of disease burden and health expenditure. As such, we assume that countries' spending is reflective of the ASCVD disease burden; however — as the results of our country-specific analyses suggested — there is a misalignment between burden and spending. While we tried to account for this by scaling our values down by using the relationship between DALYs and spending for NCDs, it could still be the case that, especially in countries with different population health priorities, spending patterns vary.

In addition, some countries and territories did not have data on either healthcare expenditure or the disease burden of ASCVD. As a result, we excluded these regions from our global analysis, resulting in a likely underestimate of the global burden of ASCVD.

As mentioned in this report's section on The estimated global burden of ASCVD, our figure including indirect costs should be interpreted with caution, as there is a paucity of data on indirect costs associated with ASCVD in general, and especially when considering low- and middle-income countries. Consequently, we used the relationship between direct and indirect costs to inform the values we estimated for other countries. Thus, it is likely that our global values including both direct and indirect costs are overestimates and should be interpreted in light of these assumptions.

Likewise, in our country-specific analyses, we faced challenges collecting data on indirect costs as they relate to ASCVD and its clinical manifestations. The steps we took to navigate these data gaps are described in Appendix 2 — Methodology: Country-level analyses. Similarly, there was very limited literature quantifying the impact of PAD; given this limitation, we assumed similar care pathways across countries to assign a monetary value to the impact of PAD. However, it is possible that patient care for PAD differs from country to country, meaning that our estimates for direct costs might not reflect the true values. In addition, the GBD Study does not include PAFs for LDL-C for PAD; as such, we utilised literature stating that the PAF for PAD related to hypercholesterolemia is 17% (Criqui and Aboyans, 2015). Ultimately, these gaps suggest that there would be value in future research aiming to quantify the productivity losses caused by ASCVD, as well as the total burden imposed by PAD and PAD-related LDL-C.

In addition, there is an issue of comparability across our country-specific analyses. That is, we used different sources from the literature to inform each country-specific estimate for the impact of ASCVD, and these sources varied in terms of their approaches, methodologies and underlying assumptions. Observed differences in ASCVD burden between countries may reflect not only true variations in disease impact but also methodological differences in how that impact was assessed. Thus, readers should exercise caution when making cross-country comparisons and consider these findings as country-specific estimates rather than standardised, directly comparable values.

Moreover, a limitation of using the GBD database is that their disease categories do not align perfectly with our analytical needs. While the GBD provides comprehensive data for IHD and IS, PAD was represented using GBD data on lower-extremity PAD, which accounts for the majority of PAD burden. This may lead to a slight underestimation of PAD prevalence—and, therefore, underestimations of its aggregate socioeconomic burden—as lower extremity PAD represents a subset of the PAD population.

For direct costs associated with PAD in Canada and the Netherlands, we assumed HCRU was equal to some average of HCRU in the United States and 5EU (i.e. France, Germany, Italy, Spain, and the UK), as limited data existed estimating HCRU in Canada and the Netherlands; it is possible that patients in different countries would follow distinct care pathways, but this approach allowed for a consistent approach across the nine countries for PAD in the absence of data. In terms of indirect PAD costs, there is limited information available on informal caregiving associated with PAD. As such, all the figures for informal caregiving for PAD were derived from literature on amputations—one of the most severe consequences of PAD—among diabetics in Portugal. Thus, we likely underestimated the burden associated with informal care among PAD patients, as we assume that only those undergoing amputation would be the recipients of such care. Methodologically, we utilised a prevalence-based approach for our country-specific analyses. As with any report or study using such an approach, our report thus does not consider heterogeneity among patients and assumes that all patients, on the average, cost the same amount — regardless of disease stage.

Finally, we rely on PAFs to isolate the LDL-C-related burden of ASCVD. However, this approach — though consistently used in academic literature — is also limited. Most significantly, PAFs represent a theoretical maximum reduction assuming complete elimination of elevated LDL-C associated risk in the population, which is neither clinically achievable nor realistic from a public health perspective. Still, these values represent an upper bound on the avoidable burden of ASCVD and offer valuable insights into the relative importance of LDL-C as a modifiable risk factor for ASCVD.

8 Conclusion

This report demonstrates that ASCVD imposes a substantial and growing socioeconomic burden globally, with high LDL-C contributing substantially to that burden. Our analysis estimates that ASCVD accounts for up to Int$680 billion in direct healthcare costs and up to Int$1.4 trillion when indirect costs are considered. Notably, up to one-third of this burden may be associated with elevated LDL-C, which is a modifiable risk factor, suggesting a significant opportunity for investment in prevention. When interpreting these values, readers should consider the limitations described in the previous section.

The results of our country-specific analyses revealed that ASCVD costs may range from US$5,400 to US$17,900 per patient annually, with indirect costs often exceeding direct healthcare costs.

The contribution of LDL-C to ASCVD's total costs reveals the potential for improved LDL-C management to reduce this burden. Indeed, improved LDL-C can be attained through better implementation of existing guidelines, increased use of LLTs, and strategic investments in prevention. These initiatives not only could align spending with disease burden but also offer the potential to improve population health, reduce hospitalisations, and address health equity concerns — particularly among underserved groups such as women and low-income populations.

Ultimately, the findings of this report reinforce the value of prevention and the critical role of LDL-C management in mitigating the global impact of ASCVD.

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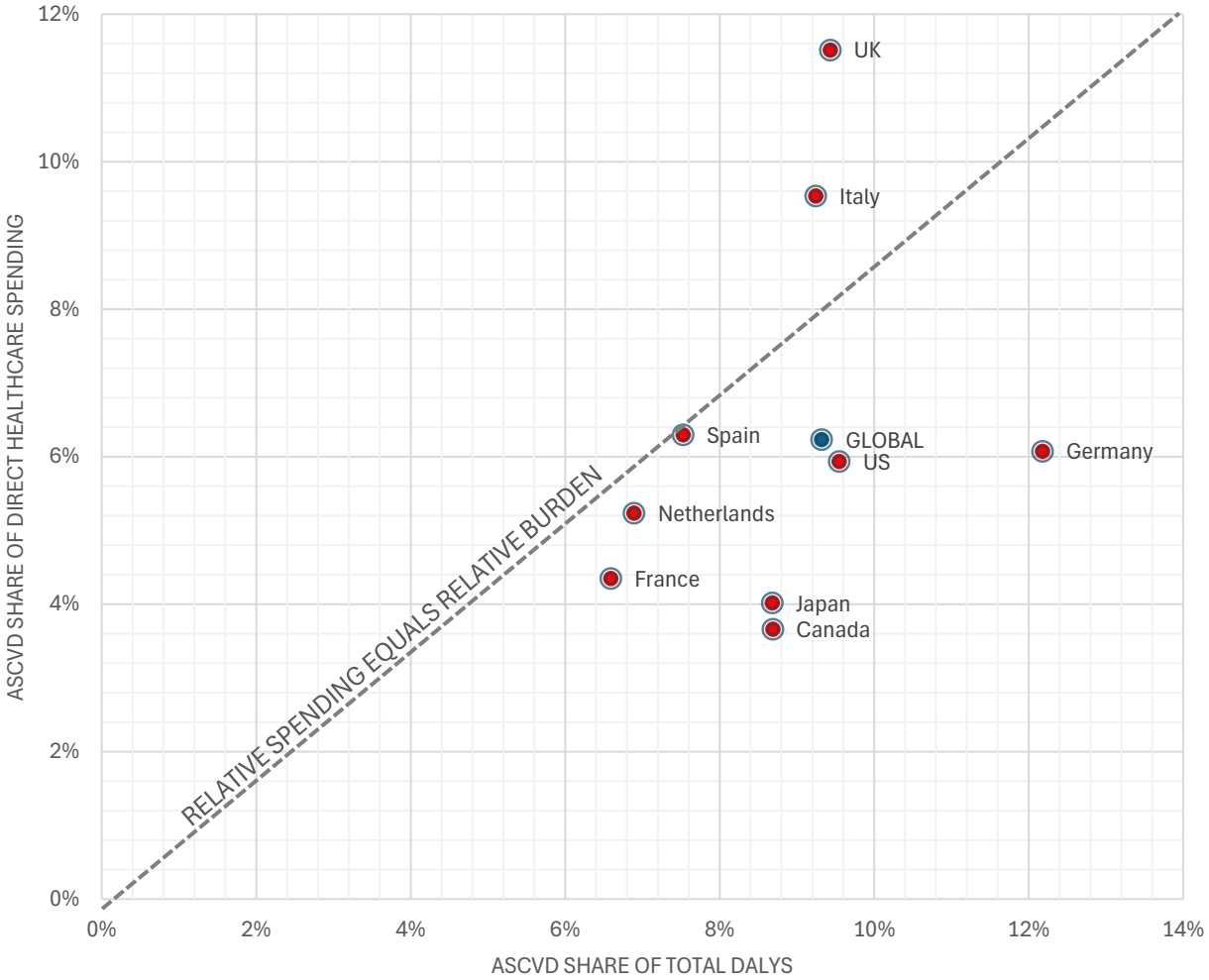
10 Appendix

10.1 Appendix I – Methodology: Global burden of ASCVD

Figure 5 Relative share of ASCVD burden vs expenditure



The data for this graph come from the GBD 2023 (Institute for Health Metrics and Evaluation (IHME), 2024) for information on DALYs, the Global Health Expenditure Database for information on total direct healthcare spending (WHO, 2023), and from our country-specific and global analyses for direct spending on ASCVD.

Figure 5 provides validation to our approach - specifically the assumption that the ratio of relative NCD burden to expenditure approximates the ratio of ASCVD burden to expenditure - since our global estimate lies amongst countries for which we have ASCVD-specific data when comparing relative share of burden and investment.

10.2 Appendix 2 – Methodology: Country-level analyses

Disease Burden

To understand the scale of impact within each country, we collected country-specific prevalence data on IHD, IS, and PAD. For this purpose, we used the 2023 Global Burden of Disease (GBD) database, which includes data on 371 diseases and injuries and 88 risk factors across 204 countries and territories (The Lancet, 2025). The GBD uses a mixed-method approach, combining thousands of data sources, such as censuses, surveys, disease-specific registries, and vital registration systems (Naghavi et al., 2025); as such, the GBD provides comprehensive disease burden estimates that are widely used in academic research (Li et al., 2024; Ji et al., 2025).

Direct Costs

We conducted a targeted literature review to understand the varying direct costs associated with each of the three sub-diseases in the nine countries of interest. We took the perspective of health systems and patients, since direct costs related to patients' healthcare resource utilisation (HCRU) may be incurred by either party. Direct costs included the costs attributable to physician visits (both primary care and outpatient visits), A&E care, inpatient hospitalisations, and medication use.

Generally, comprehensive literature exists on the direct costs attributable to IHD and IS in each of the nine countries. As such, we were able to use the per-patient values of direct costs from the literature to understand the country-specific burden of IHD and IS. For IS, we relied on overall cerebrovascular disease (CeVD) cost data for some countries as a proxy for IS costs, given that IS accounts for the majority of CeVD cases.

While studies estimating the burden of PAD in the US, Italy, and Japan exist, there is otherwise a paucity of literature on the costs owed to PAD in the relevant countries. To overcome this gap, we leaned on a Marrett et al. (2013) paper that captures HCRU among patients with PAD in the United States and 5EU (France, Germany, Italy, Spain, and the UK). We used the average patient HCRU and collected the country-specific healthcare unit costs to generate an estimate of the average per-patient cost of PAD in each country. For countries excluded from the Marrett et al. (2013) paper (i.e. Canada and the Netherlands), we assumed that HCRU was equal to some average of those included in the paper. Ultimately, this is a limitation of this report, as it is possible that patients in other countries follow different care pathways than those in the 5EU and the United States. However, this approach allowed for a consistent methodology across the nine countries for PAD.

To derive aggregate direct costs for IHD, IS, and PAD, we multiplied the average per-patient costs of each sub-disease by its respective prevalence. We inflated all values to 2021 costs. For PAD, diagnosed prevalence was used rather than overall prevalence, given PAD's substantial rates of underdiagnosis—50% of PAD patients are asymptomatic leading to low recognition and undertreatment by clinicians (Shu and Santulli, 2018). Proportions with symptomatic lower extremity PAD from GBD 2017 were used as proxies for diagnosis and applied to overall prevalence from GBD 2023 to generate diagnosed prevalence estimates (Institute for Health Metrics and Evaluation, 2024; James et al., 2018). For IHD and IS, GBD prevalence values were well aligned with diagnosed prevalence in the literature, so no adjustments were made.

In Table 4, we provide a comprehensive list of the literature sources from which we derived our values, as well as where we leaned on our own calculations and assumptions to generate direct costs.

Table 4 Direct cost calculations and assumptions

SUB-DISEASE	COUNTRY	METHOD & SOURCES
ISCHEMIC HEART DISEASE	United States	All costs are directly from Kazi et al. (2024) and the supplementary material.
	Canada	Hospitalisation costs due to IHD were from Smolderen et al. (2010). All other costs were derived from Tarride et al. (2009), from which we used proportions relating other direct medical costs (e.g., medicine costs and physician visits) to the cost of hospitalisations, thereby providing us with estimates of each direct cost component
	United Kingdom	All costs were directly from Landeiro et al. (2024) and scaled according from the relative disease burden in England to the rest of the UK using GBD data (Institute for Health Metrics and Evaluation, 2024).
	Netherlands	All costs are directly from source (Luengo-Fernandez et al., 2023).
	Germany	All costs are directly from source (Luengo-Fernandez et al., 2023).
	France	All costs are directly from source (Luengo-Fernandez et al., 2023).
	Italy	All costs are directly from source (Luengo-Fernandez et al., 2023).
	Spain	All costs are directly from source (Luengo-Fernandez et al., 2023).
	Japan	All costs are directly from source (Gochi et al., 2018).
CEREBROVASCULAR DISEASE	United States	All costs are directly from Kazi et al. (2024) and the supplementary material.
	Canada	All costs are directly from Vyas et al. (2023), assuming Ontario is representative of costs and treatment pathways in Canada.
	United Kingdom	All costs were directly from Landeiro et al. (2024) and scaled according from the relative disease burden in England to the rest of the UK using GBD data (Institute for Health Metrics and Evaluation, 2024).
	Netherlands	All costs are directly from source (Luengo-Fernandez et al., 2023).
	Germany	All costs are directly from source (Luengo-Fernandez et al., 2023).

	France	All costs are directly from source (Luengo-Fernandez et al., 2023).
	Italy	All costs are directly from source (Luengo-Fernandez et al., 2023).
	Spain	All costs are directly from source (Luengo-Fernandez et al., 2023).
	Japan	All costs are directly from source (Matsumoto et al., 2017).
PERIPHERAL ARTERIAL DISEASE	United States	All costs are directly from source (Scully et al., 2018).
	Canada	Used the average of HCRU between the 5EU and US from Marrett et al. (2013), and applied unit costs from the Canadian Institute for Health Information (2024b; a) and Smolderen et al. (2010).
	United Kingdom	Used the HCRU from the 5EU from Marrett et al. (2013) and applied unit costs from the UK Unit Costs of Health and Social Care 2022 Manual (Jones et al., 2022) and applied an average of the hospitalisation costs attributable to PAD from France and Germany (Smolderen et al., 2012). For medication costs, applied an average of the PAD medication costs in France (Emery et al., 2020) and Italy (Mennini et al., 2024) and scaled that value by the difference in healthcare spending between the average of France and Italy and the UK (World Health Organization, 2025a).
	Netherlands	Used the HCRU from the 5EU from Marrett et al. (2013) and applied unit costs from Luengo-Fernandez et al. (2023) and Peters et al. (2025). For medication costs, applied an average of the PAD medication costs in France (Emery et al., 2020) and Italy (Mennini et al., 2024) and scaled that value by the difference in healthcare spending between the average of France and Italy and the Netherlands (World Health Organization, 2025a).
	Germany	Used the HCRU from the 5EU from Marrett et al. (2013) and unit costs from Luengo-Fernandez et al. (2023) and Smolderen et al. (2012). For medication costs, applied an average of the PAD medication costs in France (Emery et al., 2020) and Italy (Mennini et al., 2024) and scaled that value by the difference in healthcare spending between the average of France and Italy and Germany (World Health Organization, 2025a).
	France	Used the HCRU from the 5EU from Marrett et al. (2013) and unit costs from Luengo-Fernandez et al. (2023) and Emery et al. (2020).
	Italy	All costs taken directly from source (Mennini et al., 2024).

Spain	Used the HCRU from the 5EU from Marrett et al. (2013) and unit costs from Luengo-Fernandez et al. (2023). For medication costs, applied an average of the PAD medication costs in France (Emery et al., 2020) and Italy (Mennini et al., 2024) and scaled that value by the difference in healthcare spending between the average of France and Italy and Spain (World Health Organization, 2025a).
Japan	All costs taken from source (Hosaka et al., 2014).

Indirect Costs

ASCVD—and, therefore, elevated LDL-C—impose significant costs on healthcare systems; however, they also have broader economic impacts that must also be quantified to capture their full socioeconomic burden. We separate this impact into three types of indirect costs: productivity losses due to premature mortality or retirement, productivity losses owed to morbidity, and the burden due to informal care. As with direct costs, we inflated all costs to 2021 values, and where net present values were calculated, we used a discount rate of 3.5%

Productivity losses of premature mortality or retirement

A significant driver of indirect costs is the productivity losses due to premature mortality or retirement. That is, when an individual dies before retirement or retires early, society loses all the future economic output that person would have generated through their remaining working years.

To monetise this value, we reviewed the literature related to IHD, IS, and PAD in each country; where this value was quantified, we used the per-patient values from the literature in our analysis. Where this information was not available, we utilised data from the GBD on annual deaths decomposed by age group (Institute for Health Metrics and Evaluation, 2024). We found the yearly number of deaths below each country's retirement age for IHD, IS, and PAD, and we discounted the future earnings that would have been made in the absence of death to present values. Table 5 describes where we utilised values from the literature, and where we calculated values ourselves, as well as what assumptions we made.

Productivity losses due to morbidity

Productivity losses are also generated through morbidity; that is, there is an economic impact when a health condition reduces people's ability to work, even if they remain alive and in the workforce. The manifestations of productivity losses due to morbidity are absenteeism—taking sick days—and presenteeism—working at a reduced capacity due to illness. In addition, we considered early retirement under productivity losses due to morbidity.

Our approach utilised disease- and country-specific productivity loss values from existing academic literature as the primary data source. Where such estimates were not available in the literature, we employed work impairment data and applied the human capital approach (HCA), using average wages in each country to derive monetary valuations of presenteeism and absenteeism costs for IHD, IS, and PAD. The data sources and calculation methodologies are documented in Table 5.

To estimate losses owed to premature retirement, we utilised a similar approach to premature mortality; we used data on the proportion of people in each age group who did not return to work following major cardiovascular events. However, we excluded early

retirement effects for PAD due to insufficient literature evidencing PAD's impact on retirement. Table 5 describes where we used values directly from the literature, and where we calculated these values ourselves—along with the assumptions and sources we used to inform these calculations.

Burden of informal care

Finally, the third component of indirect costs that we include in this analysis is informal carer burden—that is, the economic value of the unpaid care provided by family members, friends and other non-professional caregivers to individuals with ASCVD.

Again, we reviewed the relevant academic literature for country-specific quantifications of the informal care burden attributable to each disease. Where per-patient informal care costs were available, we used these values. In their absence, we employed disease-specific estimates of informal care hours and applied the HCA for monetary valuation. When neither cost estimates nor informal care hours were available for the overall disease, we used informal care estimates for major clinical events associated with each condition (e.g., amputations for PAD) or relied on assumptions on the relationship between informal care costs and indirect costs more broadly. Table 5 details where different methods were used to ascertain these values.

Table 5 Indirect cost calculations and assumptions

SUB-DISEASE	COUNTRY	METHOD & SOURCES
ISCHEMIC HEART DISEASE	United States	Productivity losses from morbidity and mortality are directly from Kazi et al. (2024) and its supplementary material. Informal care hours per year are from Dunbar et al. (2018), with the hourly wage from home health and personal care aides used to monetise this value (Bureau of Labor Statistics, 2023).
	Canada	Estimated productivity losses using a Tarride et al. (2009) paper suggesting that 63% of all CVD costs in Canada are caused by productivity losses, assuming that this relationship holds for IHD. For informal caregiving, we used the relationship between the total costs of informal caregiving across all disease areas and total health expenditure (Shearkhani et al., 2025), and we applied that ratio to the direct cost of IHD, assuming that relationship between informal caregiving and spending for IHD is reflective of this relationship across all diseases.
	United Kingdom	All indirect costs were taken directly from Landeiro et al. (2024) and scaled according from the relative disease burden in England to the rest of the UK using GBD data (Institute for Health Metrics and Evaluation, 2024).
	Netherlands	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).
	Germany	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).
	France	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).

	Italy	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).
	Spain	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).
	Japan	Productivity losses due to mortality and morbidity are from Gochi et al. (2018). We estimated informal care costs by calculating the ratio of CVD DALYs attributable to IHD using the GBD (Institute for Health Metrics and Evaluation, 2024). We also estimated the ratio of direct spending on CVD owed to IHD (Matsumoto et al., 2017; Gochi et al., 2018). Using the average of these ratios, we applied this to the total cost of informal giving for CVD, thereby obtaining an estimate of the cost of informal caregiving for IHD (Matsumoto et al., 2017).
CEREBROVASCULAR DISEASE	United States	All productivity losses are from literature (Kazi et al., 2024). Costs associated with informal caregiving are from Dunbar et al. (2018), which provides the hours spent caring for patients with stroke. We multiplied these values by the average wage for personal care aides to obtain a monetary value for this time (Bureau of Labor Statistics, 2023).
	Canada	We used the GBD to estimate the number of fatal and non-fatal ischemic strokes each year (Institute for Health Metrics and Evaluation, 2024; Yu et al., 2024). We estimated the number of stroke survivors who return to work within 1 and 2 years (Duong, 2024), and, using a small study that suggested that stroke survivors who return to work tend to miss 53 days of work through both absenteeism and presenteeism, applied the human capital approach to calculate a monetary value for these productivity costs associated with morbidity (Wein et al., 2021). Likewise, for those who do not return to work and for fatal strokes, we applied a human capital approach, multiplying the years that each person would have worked by the average wage in Canada, and discounting this value by 3.5% (Statistics Canada Government of Canada, 2018).
	United Kingdom	All indirect costs are directly from Landeiro et al. (2024) and scaled according from the relative disease burden in England to the rest of the UK using GBD data (Institute for Health Metrics and Evaluation, 2024).
	Netherlands	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).
	Germany	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).
	France	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).
	Italy	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).

	Spain	All indirect costs are directly from source (Luengo-Fernandez et al., 2023).
	Japan	All indirect costs are directly from source (Matsumoto et al., 2017).
PERIPHERAL ARTERIAL DISEASE	All countries	Calculated productivity losses attributable to morbidity by using results from the work impairment survey due to PAD (this was measured in the US, and the EU5—UK, France, Germany, Spain, Italy) (Marrett, DiBonaventura and Zhang, 2013). We assumed that Canada had the average of the EU5 and US, that the Netherlands had the same work impairment as the EU5, and that Japan had the same work impairment as the average of the EU5 and the US. We took the prevalent cases in each country and multiplied this by relevant employment rates to generate the number of prevalent cases of PAD among the employed population. We multiplied the average yearly salary by the impairment at work attributable to PAD, and we then multiplied this figure by the number of prevalent cases among the employed population. There is very limited information on informal caregiving associated with PAD. As such, we only looked at losses associated with amputations. All the figures for informal care for amputation came from literature on diabetics in Portugal—e.g., patients dependent on informal caregivers, hours spent with patients (Costa, Machado and Pereira, 2020; Costa et al., 2020). We applied percentages of PAD patients who undergo an amputation using literature from Bonaca et al. (2021). We then took prevalent cases of PAD in each country, multiplied by the probability of amputation in a year, and multiplied by the percentage of people undergoing amputation that require informal care and the hours of informal care per year. To monetise this value, we applied the hourly wage in each country.

Applying PAFs

PAFs are calculated using the following equation:

$$\text{PAF} = \frac{\text{p}(\text{RR} - 1)}{\text{p}(\text{RR} - 1) + 1}$$

where p = prevalence of exposure and RR = relative risk of disease outcome associated with exposure to the risk factor.

The equation above shows that PAFs are an increasing function of the proportion of a population exposed to a certain risk factor—in this case, elevated LDL-C—and the relative risk of a disease outcome given exposure.

Elevated LDL-C is defined by the GBD as any level of LDL-C that increases the risk of certain disease outcomes (DALYs, YLDs or deaths) and is above the LDL-C levels associated with the minimum level of risk—i.e. the theoretical minimum risk exposure level (TMREL) (Brauer et al., 2024). The TMREL in the GBD 2023 is defined as 0.9-1.4 mmol/L (34.8-54.1 mg/dL). We utilised PAFs grounded in this definition of elevated LDL-C, ensuring we capture the full range of burden associated with LDL-C rather than only the burden associated with more extreme clinical categories.

When calculating the LDL-C-attributable cost, we multiplied each disease cost by disease and country-specific PAFs. We used YLD PAFs from GBD 2023 in our analysis given YLDs are a measure of morbidity, which contributes to the economic burden of disease (Institute for Health Metrics and Evaluation, 2024).

For the UK-specific analysis, calculating the burden of LDL-C at different thresholds, we required information on the LDL-C prevalence distribution and relative risks of disease outcomes for each LDL-C range. The prevalence distribution across LDL-C levels is sourced from the GBD 2021 (Institute for Health Metrics and Evaluation, 2024). To calculate a relative risk distributions, we utilised data from Ference et al. (2012), a meta-analysis of Mendelian Randomisation studies that found long-term exposure of lower LDL-C was associated with a 54.5% reduction in likelihood of IHD cases per mmol/L. This reduction is applied to all ASCVD in Ference et al. (2017) and we follow the same approach. These inputs were used to estimate LDL-C level-specific PAFs, which were then applied to the UK economic burden estimate to estimate the contribution of different LDL-C categories.

Multimorbid Patients

Some patients will have more than one of the ASCVDs, which can lead to healthcare costs or productivity costs that are either less than or greater than the sum of the individual disease costs—that is, multimorbid costs may be 'sub-additive' or 'super-additive' relative to the simple sum of the per-patient costs associated with either disease. If costs are sub-additive, not accounting for multimorbidity leads to an overestimation of costs; in the case of super-additivity, failing to account for multimorbidity underestimates costs.

To account for multimorbidity, we take the following steps:

1. **Identification of specific multimorbidities and their prevalence** — We selected multimorbidities based on two key criteria:

    i. **Prevalence numbers** — The multimorbidity should be sufficiently prevalent to be considered in our analysis.

    ii. **Additivity** — If costs are additive (e.g., the burden of a patient who is comorbid in PAD and IHD is equal to the sum of the burden of these diseases), it is not necessary to consider the cost of multimorbidity separately.

    All paired combinations of IHD, IS, and PAD were deemed to satisfy these criteria. We estimated prevalence based on proportions of multimorbid patients in the REACH registry (Suárez et al., 2010). Multipliers to reflect the non-additivity of disease costs were calculated using data in Mahoney et al. (2008). All multimorbid costs were sub-additive, meaning the multimorbid cost was smaller than the sum of the two single disease costs.

2. **Creation of separate multimorbid disease categories** — We subtracted multimorbid patients from the prevalence estimates of each single disease and created separate multimorbid diseases categories to ensure patients were not double-counted.

3. **Calculation of unit costs associated with multimorbidities**:

    - **Direct costs** — Multimorbid-specific unit costs depended on multipliers applied to the sum of two diseases. The multiplier reflected the subadditivity of multimorbid ASCVDs in Mahoney et al. (2008).

- **Indirect costs** — The cost applied was the most expensive indirect 'unit cost' of each of the two involved diseases. We conservatively assumed no additional impact of multimorbid conditions on absenteeism, presenteeism or informal care hours.

4. **Calculation of weighted average PAFs** — These were calculated using weights aligned with the relative cost contribution of each disease towards the multimorbid unit cost(s). Since the PAF reflects the avoidable multimorbid disease burden attributable to elevated LDL-C, the overall effect of reducing LDL-C falls between the two PAFs, with larger reductions observed in diseases with higher PAFs and smaller reductions in those with lower PAFs.

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