20 Cholesterol, saturated fats and trans fats

Burden, epidemiology and priority interventions

Roger Darioli, Pascal Bovet, Nick Banatvala, Kay-Tee Khaw

Unhealthy levels of blood lipids, which are largely associated with an unhealthy diet (particularly saturated fats and trans fat), are a strong cause of atherosclerosis and high blood cholesterol level is a main modifiable metabolic risk factor of cardiovascular disease (CVD), particularly ischaemic heart disease (IHD). Interventions promoting a healthy diet in the whole population can improve population levels of blood lipids, while several blood cholesterol-lowering medications are highly effective among individuals with a high CVD risk.

Dietary fats provide energy as well as essential fatty acids and fat-soluble vitamins. From a health perspective, two major types of fats in food are of particular relevance: *saturated fats* and *unsaturated fats* (monounsaturated or polyunsaturated). High overall fat intake may be associated with excessive total energy intake as there are nine calories in every gram of fat, regardless of the type of fat (i.e. over twice the amount of calories per gram of carbohydrate or protein).

BOX 20.1 DIETARY FATS AND CHOLESTEROL AND THEIR RELATIONSHIPS TO CARDIOVASCULAR RISK

Saturated fats: high concentrations are found in animal products such as meat and dairy products and some vegetable oils (e.g. palm oil which accounts for a third of all oil consumed globally, and coconut oil). Saturated fats are generally detrimental to health in large amounts (e.g. >10% of total dietary intake), mainly because they increase the levels of blood cholesterol. However, the relationships between levels, types and sources of saturated fats on health, and their interaction with broader dietary habits, are a complex area of science and public health[1] and are not described further in this chapter.

Unsaturated fats: foods with a high content include most vegetable oils, as well as nuts, seeds and oily fish. Unsaturated fats (monounsaturated or

DOI: 10.4324/9781003306689-23

polyunsaturated) are not generally detrimental to cardiovascular health (except trans fats).[2]

Trans fats (also called trans fatty acids): a particular type of unsaturated fats. Natural trans fat is present in low levels (<5%) in the meat and dairy products of ruminant animals. However, most dietary trans fat intake comes from the industrial processing of unsaturated fat to give food a longer shelf life and make the fat more resistant to heating (e.g. allowing oil to be used repeatedly for frying). Industrially-produced trans fat occurs in substantial proportions (e.g. 5–30%) in fried and baked foods (e.g. doughnuts, cakes, pie crusts, biscuits, frozen pizza, cookies, crackers) and margarines. Trans fat is a major cause of atherosclerosis, with a 23% higher risk of IHD for each 2% increase in calories from trans fat.

Cholesterol: a lipid essential to building healthy cells and a precursor of several hormones and steroids. Dietary intake of saturated fats increases the *de novo* production of cholesterol by the body (particularly in the liver) and increases blood cholesterol levels. Dietary intake of cholesterol (e.g. from eggs) has a relatively small role in blood cholesterol levels and CVD risk.[3] High blood cholesterol is the main cause of atherosclerosis and CVD.[4]

Triglycerides: Most of the fats we eat are in the form of triglycerides (TG). They are carried in the blood and used to provide and store energy. TG is also formed in the body from excess calories, alcohol and sugar. High blood TG levels are often a sign of other conditions that increase the risk of IHD,[5] including obesity and metabolic syndrome — a cluster of conditions that includes too much fat around the waist, high blood pressure, high blood TG, low blood HDL-cholesterol, and high blood glucose.

Blood lipids and their relationships to cardiovascular risk

Cholesterol is not water-soluble and is therefore transported in the blood 'attached' to large water-soluble lipoproteins. Around ~80% of all cholesterol in the blood is 'attached' to low-density lipoproteins (LDL): this is the 'LDL-cholesterol' (LDL-C). High blood LDL-C is strongly associated with atherosclerosis and a *higher* risk of CVD, and it is therefore called 'bad cholesterol'. Trials of interventions with statins showed that a reduction of 1 mmol/L (38.7 mg/dL) in LDL-C – in line with an average effect of a low-dose statin treatment- reduces the risk of IHD by 33%.[6] The blood level of 'total cholesterol' (TC) is a good proxy of LDL-C since ~60-80% of all cholesterol in the blood is attached to LDL.

A substantial proportion of cholesterol in the blood (e.g. ~10–30%) circulates in high-density lipoproteins (HDL), which act to remove cholesterol from arterial walls. A high blood level of HDL-C is associated with a *lower* CVD risk and is therefore called 'good cholesterol'. However, trials of medications that increase blood levels of HDL-C have shown no significant reduction in CVD.[7]

Factors associated with unhealthy blood lipid levels (dyslipidaemia)

In addition to an unhealthy diet, abnormal levels of blood lipids (particularly increased levels of TG and decreased levels of HDL-C) are associated with obesity, tobacco use, physical inactivity, diabetes, hypothyroidism and chronic kidney disease. Familial hypercholesterolemia is a genetic condition that affects ~0.3% of the population and which is strongly associated with a premature heart attack.[8]

Disease burden (LDL-C and trans fat)

Approximately 4.4 million (7.8%) of all deaths worldwide were estimated to be attributable to elevated *LDL-C* in 2019, an increase from 3.0 million (6.4%) in 1990 (Table 20.1). These proportions decreased between 1990 and 2019 in high-income countries (HICs) and upper-middle-income countries (MICs) but increased in lower MICs and low-income countries (LICs), partly because

Table 20.1 Mortality attributable to high blood LDL-cholesterol and diet high in trans fat (IHME)

	Global		*HICs*		*Upper MICs*		*Lower MICs*		*LICs*	
	1990	*2019*	*1990*	*2019*	*1990*	*2019*	*1990*	*2019*	*1990*	*2019*
Metabolic risk: high LDL-C										
Proportion of all deaths (%)	6.4	7.8	14.0	8.0	6.9	9.6	3.9	7.2	1.3	2.7
Age-standardized mortality (per 100,000)	89	56	95	34	86	63	85	73	50	49
Diet high in trans fat										
Proportion of all deaths (%)	1.0	1.1	2.2	1.3	0.9	1.1	0.75	1.27	0.2	0.3
Age-standardized mortality (per 100,000)	13.5	8.2	14.5	5.6	10.8	7.3	15.2	12.6	7.4	6.2

of aging populations. However, the age-adjusted mortality rates (per 100,000 population) attributable to high LDL-C *decreased* in all regions between 1990 and 2019, and the decrease was much larger in HICs (a threefold decrease) than in low- and middle-income countries (only a ~20-30% decrease). This partly reflects a larger decrease in dietary intake of saturated fat (e.g. shift from whole to skimmed milk, or from meat to poultry) and better prevention and control of health outcomes (e.g. IHD) in HICs than in LICs. Correspondingly, the prevalence of high LDL-C (or that of high total cholesterol), often in the range of 10-30% among adults in HICs, has decreased in many, but not all, countries.[9] Approximately 85% of deaths related to increased LDL-C were caused by IHD and 15% by stroke (IHME).

High dietary trans fat accounted for approximately 645,000 deaths (1.1%) worldwide in 2019 (IHME). The age-adjusted mortality rates attributable to trans fats decreased in all regions between 1990 and 2019 and were lowest in 2019 in HICs, where policies to ban or limit industrially-produced trans fat have been increasingly widely implemented[10] and prevention and control of CVD developed. Virtually all of these deaths are due to IHD (IHME).

Interventions at the population level

Interventions around diet, physical activity, obesity, tobacco and alcohol are described in other chapters. WHO effective and recommended interventions that reduce unhealthy diet and can reduce LDL-C and TG blood levels include the following:

- Eliminate industrial trans fat through the development of legislation to ban their use in the food chain.
- Reduce sugar consumption through effective taxation on sugar-sweetened beverages.
- Implement policies such as subsidies to increase the intake of fruits and vegetables.
- Replace trans fat and saturated fat with unsaturated fats through reformulation, labelling, fiscal policies or agricultural policies.
- Limit portion and package size to reduce energy intake and the risk of being overweight or obese.
- Implement nutrition labelling to reduce total energy intake, sugars, sodium and fats, including displaying proportions of total fat and saturated fat, preferably with interpretive information (e.g. traffic light or equivalent systems).
- Implement nutrition education and counselling in different settings (e.g. schools, workplaces, hospitals) to increase the intake of fruits and vegetables as part of a healthy diet.
- Implement mass media campaigns on healthy diets, including social marketing to reduce the intake of total fat, saturated fats, sugars and salt, and promote the intake and fruits and vegetables.

The WHO REPLACE package provides a strategic approach to support countries in reducing trans fat in manufactured food, with the goal of global elimination by 2023.[11] The package includes six actions of action to:

- **RE**view dietary sources of industrially-produced trans fat and the landscape for required policy change;
- **P**romote the replacement of industrially-produced trans fat with healthier fats and oils;
- **L**egislate or enact regulatory actions to eliminate industrially-produced trans fat;
- **A**ssess and monitor trans fat content in the food supply and the changes in trans fat consumption in the population;
- **C**reate awareness of the negative health impact of trans fat among policymakers, producers, suppliers and the public; and
- **E**nforce compliance with policies and regulations.

Interventions at the individual level

Screening. Recommendations vary on who should be screened for high blood cholesterol and how often. The US Preventive Services Task Force for example recommends screening for all people aged 40 to 75 years.[12] Most guidelines recommend that screening is offered to individuals at high risk of CVD (e.g. those with diabetes or with a family history of CVD or high blood cholesterol, including familial hypercholesterolaemia).

Assessing blood lipids. LDL-C is the main marker of interest for CVD risk and can be measured either directly or calculated with the Friedewald formula as = TC minus HDL-C minus TG/2.2 (in mmol/l). Ideally, a complete 'lipid panel' (TC, LDL-C, HDL-C and TG) should be assessed to guide personalized management of patients with dyslipidaemias. Measurement of TC alone is a useful proxy measure of LDL-C where a complete lipid profile cannot be done. Most CVD risk score calculators require information on at least one blood cholesterol marker, e.g. total cholesterol, LDL-cholesterol or LDL-C/HDL-C ratio). Table 20.2 displays blood lipid level categories commonly considered by leading cardiology societies.

Counselling

All individuals who have abnormal blood lipid levels should be advised to adopt a healthy diet, engage in regular physical activity, abstain from using tobacco and maintain a normal weight. Further details are provided in chapters on these risk factors.

Assessing CVD risk

It is important to determine an individual's total (absolute) CVD risk (using CVD risk score calculators) in order to identify individuals who will benefit

Table 20.2 CVD risk categories associated with abnormal blood lipid levels in mmol/l (mg/dl in parentheses)

CVD risk category	*TC*	*LDL-C*	*HDL-C*	*TG*
Desirable/optimal	<5.2 (<200)	<2.6 (100)	High >1.6 (60)	<1.7 (150)
Near or above optimal		2.6–3.3 (100–129)		
Borderline high	5.2–6.2 (200–239)	3.3–4.1 (130–159)		1.7–5.7 (150–499)
High	≥6.2 (240)	4.1–4.9 (60–190)		5.7–11.4 (500–999)
Very high	≥7.5 (290)	>4.9 (190)	Low <1.0 (40)	≥11.4 (1000)

Grundy SM et al. 2019 Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;139:e1082–143.
Visseren FLJ et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227–37.

most from cholesterol-lowering treatment (i.e. those for whom the absolute CVD risk would decrease by a large amount). National guidelines need to take into account resource availability when making recommendations for pharmacologic therapy.

Pharmacological treatment

Treatment to reduce LDL-C (or TC) should be offered to individuals of all ages who have a high CVD risk, including individuals with very high LDL-C levels or who have had a CVD event, and most individuals with diabetes. Chapter 7 on CVD provides more details. Cholesterol-lowering medications are highly effective in reducing blood TC, LDL-C levels and cardiovascular mortality.[13] Statins (HMG-CoA reductase inhibitors) can safely reduce LDL-C by up to 50–60% and are the first-line medication to treat elevated TC/LDL-C blood levels. Generic statins can be fairly inexpensive (e.g. <0.1 US$ per day). Other lipid-lowering drugs include fibrates and bile acid sequestrants (e.g. cholestyramine, questran), but they are less effective than statins and have more side effects than statins. Lipid-lowering medications are generally safe, but myalgia can occur in 1–5 % of those taking statins.[14] When blood levels of TC/LDL-C cannot be sufficiently lowered with a statin alone at maximum dosage, it is possible, where resources allow, to use, in addition to a statin, another cholesterol-lowering drug, such as cholesterol absorption inhibitors (e.g. ezetimibe) or weekly/monthly injectable monoclonal antibody inhibitors of the proprotein convertase subtilisin/kexin 9 (PCSK9 inhibitors, e.g. evolocumab, alirocumab), which are highly effective but expensive.

New cholesterol-lowering medications continue to be developed, including therapies that can be taken less frequently (e.g. monthly) and could increase compliance.[15]

Although this chapter does not address the management of high blood TG, hypertriglyceridaemia is often sensitive to diet (e.g. a diet restricted in sugar and alcohol) and responds fairly well to some medications (including statins and fibrates). Guidelines on the treatment of blood lipids provide more detail on this.

The aim of blood lipid treatment should be to reduce LDL-C by >30% in patients at intermediate CVD risk and by >50% in patients at high or very high CVD risk, depending on available resources. In secondary prevention, an increasing number of guidelines, e.g. the American Heart Association and the European Society of Cardiology, recommend a very low LDL-C target (e.g. 1.8 mmol/l [<70 mg/dl]), which often requires the use of several cholesterol-lowering medications (again, depending on available resources).

Adherence and response to treatment should be evaluated at 1–3 month intervals after starting cholesterol-lowering therapy. Once acceptable levels of LDL-C (or TC) are achieved, monitoring can be reduced to 6–12 monthly intervals. Many studies show large treatment gaps in all countries, with many patients not getting the treatment they require because it is not available, not included in local guidelines, not affordable or not prioritized, and because too often long-term adherence to treatment is suboptimal (e.g. as low as <40%).[16,17] There is an increasing interest in combining lipid-lowering and blood-pressure-lowering medications (and aspirin in secondary prevention) in the form of a one polypill regimen daily, which can simplify treatment, improve adherence and reduce CVD risk at least as well as usual care.[18]

Monitoring

Indicators from the WHO Global Monitoring Framework directly related to blood lipids include:

Biological risk factors.	Age-standardized prevalence of raised TC among persons aged 18+ years (TC ≥5.0 mmol/l or 190 mg/dl); and mean TC concentration.
National health response.	Proportion of eligible persons (age 40+ with a ten-year CVD risk ≥30%, including those with existing CVD) receiving drug therapy and counselling (including glycaemic control) to prevent heart attacks and strokes.
National health response.	Availability and affordability of quality, safe and efficacious essential NCD medicines, including generics, and basic technologies in both public and private facilities.
Additional indicators.	Adoption of national policies that limit saturated fatty acids and virtually eliminate trans fats in the food supply.

Surveys on the quality of health care are useful to enhance the adherence of health professionals to guideline recommendations and benchmarking of care providers.[19]

Notes

1 Forouhi NG et al. Dietary fat and cardiometabolic health: evidence, controversies, and consensus for guidance. *BMJ* 2018;361:k2139.
2 Saturated fats and health. Scientific Advisory Committee on Nutrition, Public Health England, 2019.
3 Tobias DK. What eggsactly are we asking here? Unscrambling the epidemiology of eggs, cholesterol, and mortality. *Circulation* 2022;145:1521–23.
4 Libby P et al. Atherosclerosis. *Nat Rev Dis Primers* 2019;5:56.
5 Burgess S et al. Mendelian randomization to assess causal effects of blood lipids on coronary heart disease: lessons from the past and applications to the future. *Curr Opin Endocrinol Diabetes Obes* 2016;23:124–30.
6 Silverman MG et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;316:1289–97.
7 Woudberg NJ et al. Pharmacological Intervention to modulate HDL: what do we target? *Front Pharmacol* 2018;8:989.
8 Akioyamen LE et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. *BMJ Open* 2017;7:e016461.
9 NCD Risk Factor Collaborators (NCD-RisC). Repositioning of the global epicentre of non-optimal cholesterol. *Nature* 2020;582:73–7.
10 Nagpal T et al. Trans fatty acids in food: a review on dietary intake, health impact, regulations and alternatives. *J Food Sci* 2021;86:5159–74.
11 REPLACE trans fat: an action package to eliminate industrially produced trans-fatty acids. WHO, 2019.
12 Mangione CM et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force Recommendation Statement. *JAMA* 2022;328:746–53.
13 Silverman MG et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;316:1289–97.
14 Alonso R et al. Diagnosis and management of statin intolerance. *J Atheroscler Thromb* 2019;26:207–15.
15 Wilkins JT et al. Novel lipid-lowering therapies to reduce cardiovascular risk. *JAMA* 2021;326:266–67.
16 Chowdhury R et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013;34:2940–48.
17 Marcus ME et al. Unmet need for hypercholesterolemia care in 35 low- and middle-income countries: a cross-sectional study of nationally representative surveys. *PLoS Med* 2021;18:e1003841.
18 Yusuf S et al. Polypill with or without aspirin in persons without cardiovascular disease. *NEJM* 2021;384:216–28.
19 Aktaa S et al. European society of cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. *Eur Heart J Qual Care Clin Outcomes* 2020;26:qcaa069.