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The effects of saturated fat intake from dairy on CVD markers: the role of food matrices

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CVD is the leading cause of death worldwide, and is commonly associated with modifiable risk factors. Most studies to date examining link between food intake and risk of CVD, have focused on modulation of plasma cholesterol concentrations (total cholesterol (TC), LDL-C). However, recent studies suggest LDL particle size is a more sensitive risk marker for CVD with smaller, dense LDL particles reported as more atherogenic than larger, more buoyant LDL. Although dietary guidelines recommend SFA intake of < 10 % of total energy, this does not consider food source, with recent evidence suggesting differing, sometimes beneficial, lipid responses following consumption of SFA from dairy compared to other food sources. This may be from differences in the physical food matrices, the nutrient content of the foods, and/or how these components interact with each other, described as a 'dairy matrix effect'. Dietary fat not only raises LDL-C, but also HDL cholesterol (HDL-C), associated with reduced CVD risk. HDL particles are complex emulsions of lipids, proteins and microRNAs that exhibit atheroprotective properties. In addition, HDL particles exhibit a very heterogeneous proteomic composition, dependent on a person's disease state – with a more pro-inflammatory proteome evident in patients with established CVD. This review will discuss the evidence to date on the importance of the food matrix in modulating response to dietary SFA and impact on CVD risk factors. A focus on potential biomarker properties of lipoprotein particles beyond cholesterol and current use of such biomarkers in human nutrition research will be considered.

Key words: CVD: Dairy matrix: Lipoproteins: Saturated fat

CVD is one of the leading causes of death globally, accounting for approximately 17·9 million mortalities annually[1]. CVD is the umbrella term for a group of diseases affecting the heart and blood vessels, most commonly associated with lifestyle-modifiable risk factors such as tobacco use, physical inactivity and an unhealthy diet[1]. Poor diet, in particular, is a leading risk factor, and therefore, positive dietary changes have the potential to significantly reduce the risk of CVD[2]. It is widely accepted that a high intake of dietary fat, mainly SFA and trans fats, increase LDL cholesterol (LDL-C) concentration in the blood, a major risk factor for CVD[3]. Therefore, dietary guidelines recommend that saturated fat intake should be as low as possible[4] and

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ideally < 10 % of total energy intake[5]. However, more recently, evidence suggests that more sensitive markers, such as LDL particle size, may be a better predictor of CVD[6]. In relation to saturated fat intake, the increase in LDL-C concentrations observed may be due to an increase in larger LDL particles, which are much less associated with CVD risk, than small dense LDL particles[5].

A number of randomised control trials (RCT) and cohort studies have shown a positive association between reduced SFA intake and CVD risk, particularly when SFA are replaced by PUFA[7–9]. The Scientific Advisory Committee on Nutrition (SACN) (2019) reported on the outcomes of studies substituting saturated fats in the diet and the potential effect this would have on total cholesterol (TC), LDL-C and HDL-C levels, along with subsequent CVD outcomes. Based on the evidence of available RCT, the SACN report concluded that reducing SFA intake has beneficial effects, reducing cholesterol levels and CVD risk. Furthermore, in studies replacing SFA with PUFA, there was a favourable effect on blood lipid profile and reduced CVD risk. However, there was less evidence to suggest beneficial effects of replacement with monounsaturated fats (MUFA), and further research is needed to understand the impact of carbohydrates[10]. In 2020, Hooper et al. published an updated Cochrane Review of fifteen RCT, with a minimum duration of 24 months. The included trials suggested a 21% reduction in CVD events when comparing reduced SFA intake to those with a higher SFA intake (RR 0·79, 95% CI 0·66, 0·93)[11]. Subgroup analysis, considering replacement of SFA with PUFA, suggested a 27% reduction in CVD events (RR 0·73, 95% CI 0·58, 0·92)[11]. However, when assessing all-cause mortality risk, there was little or no effect of reduced SFA intake compared to higher SFA intake. The conclusions of this review[11] and the SACN report[10] therefore support the current public health advice, to reduce intake of SFA-rich foods to < 10 % of total energy intake and replace these with unsaturated fat sources. However, more recent evidence suggests that the link between intake of saturated fat and CVD risk may not be as straightforward as considered, and as this evidence grows such recommendations may need to be reconsidered[5].

This review will examine the evidence surrounding variation in CVD risk from SFA, in particular dairy foods. There will be a focus on the importance of the 'dairy food matrix' in modulating response to dietary SFA and the associated impact on CVD risk factors. The need to consider more accurate risk markers (LDL particle size and HDL functionality) in human nutrition research will also be discussed.

Classification and types of fatty acids

Dietary fat can be classically defined as phospholipids, TAG, or sterols such as cholesterol. TAG are the predominant form of fat found in the diet, where three fatty acids are esterified to a glycerol molecule[12]. Fatty acids are hydrocarbon chains of varying lengths and degrees of unsaturation (the presence of double bonds), with a carboxyl group at one end and a methyl group at the other. Fatty acids are commonly classified based on their chain length, which can vary between two and thirty carbons in length; short (< 6 carbon atoms), medium (6–12 carbon atoms), and long-chain (> 12 carbon atoms)[13]. They are also classified according to the absence or presence of double bonds[12]. SFA have no double bonds, whereas MUFA have one double bond and PUFA have two or more[14].

Function of fatty acids

Fatty acids play a number of critical roles in the homeostasis and structure of the cell, and the whole human body[15]. Firstly, they are the main constituents of all biological membranes built into sphingolipids, phospholipids, glycolipids, and lipoproteins. The fatty acid composition of these membranes can differ and influence the physical structure ('fluidity') of the membrane, which may impact both the functional properties and movement of membrane proteins[16]. Secondly, various metabolites of fatty acids serve as essential intracellular and extracellular lipid mediators and hormones. Finally, they function as an energy source, stored in triacylglycerols[17]. Therefore, fatty acids have countless possibilities to influence cellular functions, by impacting its structure and metabolism, acting through surface proteins (G-protein-coupled receptors), intranuclear receptors or membrane transporters[15].

SFA sources

SFA are a heterogeneous group of fatty acids which contain only carbon-to-carbon single bonds[5]. As described above, one classification method for fatty acids is based on their carbon chain length, while another is based on function. The melting point of SFA increases as their chain length increases, for example those ≥ 10 carbon atoms are solid at room temperature[5]. The main dietary sources of SFA are animal products, such as meat and dairy, but they are also found in tropical oils such as palm and coconut[17]. Although most fat food sources contain a mixture to some degree of all chain lengths, very generally, they differ depending on the specific food; i.e. SFA are mainly found in dairy fats, while medium and long-chain SFA are present in red meat, dairy fats, and plant oils[18]. Within these food sources, varying proportions of different SFA are present, along with other nutrients which can play a significant role in the observed physiological and biologic effects[5]. SFA can also be produced within the body, from the precursor acetyl-CoA, derived from amino acid or carbohydrate metabolism[16].

Saturated fat and metabolic health

Research surrounding dietary fats and health, and in particular saturated fat, has centred around the harmful effects associated with a diet high in SFA[19]. Current

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Table 1. Overview of studies investigating the effects of saturated fat on metabolic health

Author	Year	Study Design	Objective	Population (*n*)	Age	Findings
de Souza *et al.*[24]	2015	Systematic review and meta-analysis (Observational)	Associations between SFA and *trans* intake and all-cause mortality, CVD and associated mortality, CHD and associated mortality, ischaemic stroke and T2DM.	90 501–339 090 (Male and Female)	≥ 18 years	SFA not associated with all-cause mortality, CVD, CHD, ischaemic stroke or T2DM.
Mente *et al.*[29]	2017	Cross-sectional analysis of PURE study	The effect of dietary nutrients on blood lipids and blood pressure.	125 287 (Male and Female)	35–70 years	Replacement of SFA with CHO associated with most adverse effects on blood lipids. Replacement of SFA with USFA improved LDL and BP but worsened HDL and Trigs.
Zhu *et al.*[28]	2019	Systematic review and dose-response meta-analysis (PCS)	Associations between dietary fat intake and CVD.	NA	> 18 years	Higher TFA intake associated with inc. risk of CVD. No associations observed between total fat, SFA, MUFA and PUFA intake, and risk of CVD.
Hooper *et al.*[11]	2020	Cochrane systematic review of RCT	Assess the effect of reducing SFA intake and replacing it with CHO, PUFA, MUFA and/or protein on mortality and CVD morbidity.	> 56 000 (Male and Female)	> 18 years	Reduced SFA may reduce CVD events, to a greater extent with greater cholesterol reduction. Reducing SFA has little or no effect on all-cause or CVD mortality.
Ho *et al.*[25]	2020	Prospective cohort study	Associations of fat and carbohydrate intake with CVD and mortality.	195 658 (Male and Female)	37–73 years	CHO intake showed a non-linear association with mortality; positive association at 50–70 % of energy intake. Higher intake of MUFA and lower intake of PUFA and SFA is associated with lower risk of mortality.
Kang *et al.*[26]	2020	Systematic review and dose-response meta-analysis (PCS)	Association between saturated fatty acid consumption and risk of stroke.	832–135 335 (Male and Female)	> 18 years	Higher consumption of SFA is associated with lower risk of stroke.
Li *et al.*[27]	2022	Meta-analysis of prospective studies	Associations between total or individual SFA biomarkers and risk of cardiometabolic diseases.	220, 590 (Male and Female)	49–79 years	Higher conc. of total SFA associated with increasing risk of cardiometabolic diseases. Risk reduced with increasing odd-chain SFA levels. Inverse relationship between C17:0 and T2D or CVD risk.

dietary recommendations were developed based on epidemiological studies which demonstrated a link between a high dietary intake of SFA and greater CVD incidence[20–22]. However, in more recent years, new evidence has emerged which questions the link between SFA intake and CVD risk, which need to be considered[9,23,24]. A number of studies (Table 1) investigating the associations between saturated fat and cardiometabolic outcomes have reported little or no effect on all-cause or CVD mortality after reducing SFA intake[11,24–29]. With regards to CVD events, however, a higher concentration of total SFA was associated with increasing risk of cardiometabolic diseases in a recent meta-analysis[27], and this was consistent with the *Hooper et al.* review[11] where a reduction in SFA was found to reduce CVD events, and to a greater extent with greater cholesterol reduction. One of the studies however, suggested an inverse linear relationship between SFA intake and stroke risk with a higher consumption of dietary SFA being associated with a lower risk of stroke[26]. While evidence of the biological mechanism behind this association remains unknown, some studies have reported an increase in HDL-C[30] and a decrease in TAG and ApoB-to-ApoA1 ratio with a higher SFA intake[31], and higher levels of circulating long-chain fatty acids (18:0, 20:0, 22:0, and 24:0) in particular, were associated with lower risk of atrial fibrillation[32]. These effects may play a role in reducing stroke risk.

Recent research has also shown that although SFA generally increases lipid and lipoprotein levels, individual SFA may have differing effects on these plasma levels[33]. A systematic review conducted by Perna and Hewlings in 2022[34], investigated the effects of SFA chain lengths on CVD development, and found that overall, long-chain SFA (C12-18) were associated with increased risk for CVD while short and medium chain (C4-C10) may be associated with neutral or favourable effects. Researchers

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did note difficulty in distinguishing between individual SFA consumption due to most food sources containing a variation of SFA[34]. In addition, researchers reported low intakes of C4-C10 across included studies, compared to longer chain fatty acids, e.g. C16 and C18. In one study, C18 was the only SFA linked to increased CVD risk[35]. However, the main source of C18 in these studies was processed meat which may suggest the food source, rather than the individual SFA, is more responsible for this effect. The inconsistencies in findings are most likely influenced by shared food sources for SFA[35–37], making it difficult to draw definitive conclusions between SFA chain lengths and CVD risk. Therefore, with respect to public health and food based dietary guidelines, recommendations cannot be made for individual fatty acids, as this fails to consider the food source and the mixture of fatty acids within.

As different SFA have varying effects on blood lipid profiles, so too do their given food source. This has shown to be the case across not only food groups, but also between foods within the same food category, such as dairy products[38]. These differences between foods that contain similar fat profiles are considered to be 'food matrix' effects, whereby the nutrients within the foods interact with the overall structure and may result in different health outcomes[38].

Saturated fat and dairy

Dairy is a significant contributor to SFA intake in the diet, both in Europe and the United States, accounting for approximately 20 % of population SFA intake[39]. Dairy foods vary considerably in their fat content, but in general, dairy fat itself contains ~60 % SFA[40]. For this reason, most current dietary guidelines tend to recommend consumption of fat-free or low-fat dairy products instead of full fat dairy. Although current recommendations surrounding SFA state that intake should not exceed 10 % of total energy, and be kept as low as possible, research is highlighting the importance of focusing on the food source (the food matrix) as opposed to individual nutrients[41]. As highlighted above, the difference in health effects between meat sources *v* dairy, with dairy derived fatty acids being associated with a lower risk of CHD when compared with meat[42]. Some research groups have expressed concern that if dietary guidelines are developed that focus on SFA content as opposed to source, nutrient-dense foods could be excluded, unintentionally resulting in lower levels of key micronutrients[23]. Dairy foods, for example, are an important source of a variety of micronutrients in the Irish diet such as calcium and vitamin B12[43], but there has been some debate regarding the classification of 'dairy foods' in dietary guidelines, with the majority recommending milk, yoghurt and cheese (low fat varieties) and excluding butter and/or cream due to their contributions to saturated and trans-fat intakes in the diet[44]. The lack of consistency across studies with regards to a universal definition of 'high' and 'low' fat makes it difficult to interpret data. In addition, categorising based on nutrient content alone (e.g. fat content), fails to consider the variability in other components and structures within the dairy food group[44]. It is these differences in the dairy matrix which may play a role in the differences in health-related outcomes between dairy foods, for example cheese *v* butter. In terms of physical structure, butter is a water-in-oil emulsion and cheese is a fermented product, where the fat is present in milk fat globules in a solid matrix[23]. A 2015 meta-analysis of RCT[45] reported consistent favourable outcomes when hard cheese was compared with butter for TC (hard cheese: reduction of 0·28 mmol/l) and LDL-C (hard cheese: reduction of 0·22 mmol/l). Their results suggest that the associations observed between dairy foods and CVD risk is driven primarily by food type (cheese, yoghurt, milk) than fat content[45].

The food matrix

Research is now showing that the link between SFA and CVD is not as straightforward as initially shown, with an emerging role for differences in the food matrix[23]. This matrix may be more influential in the effect on CVD than the absolute SFA content of the food[46]. The importance of focusing on whole foods as opposed to individual nutrients, including saturated fat, has been increasingly highlighted because of the complex physical and nutritional structure of each food, and how these different matrices may impact nutrient digestion, absorption, and bioactivity, and subsequently the biological effects from the food[41]. Dairy products are a particular example of the food matrix resulting in different health outcomes from SFA-rich food[47,48]. The main basis for the recommendation of low-fat dairy in the diet is that saturated fat raises LDL-C levels, which in turn increases one's risk of CVD[49]. However, more recent human intervention studies have investigated the potential role of the matrix when examining the health effects of dairy. A randomised controlled trial (RCT) by *Feeney et al.*[39] demonstrated the protective effect of a fermented dairy food matrix such as cheese on blood lipid concentrations. Their results show that cheese has a significant lowering effect on TC and LDL-C when compared with a deconstructed matrix of butter, protein, and calcium. This is consistent with other findings comparing cheese and butter[50–52], which also reported differential modifying effects on blood lipids when dairy fat was consumed as cheese *v* butter. These results suggest that even within dairy as a food group there is variability in its health effects, which may be due to the considerable differences in terms of structure and content[44]. For example, while cheese has a high fat content, its composition is more comparable to that of yoghurt and milk than to butter. This is due to the protein, mineral, and milk fat globule membrane (MFGM) components[40] (Table 2). High-fat dairy products are particularly rich in the MFGM, with the exclusion of butter, which loses most of the MFGM during processing, when the aqueous phase is released as buttermilk, which contains most of the MFGM[53]. This membrane protects fat globules by acting as an emulsifier and preventing enzymatic degradation[54]. Fermented dairy products such as yoghurt and cheese also contain

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Table 2. Differences in bioactive components, fat structure and protein networks of common dairy products*

Dairy food	Calcium mg/100 g	MFGM mg/100 g	Protein g/100 g, type	Fermented Y/N	Fat structure g/d	Protein network mg/d
Cheese (25 % fat)	659	150	23·2, casein	Y	MFG/aggregates/free fat	Solid/viscoelastic
Whole milk (3·5 % fat)	116	35	3·4, whey/casein	N	Native MFG or homogenised milk fat droplets/potential MFGM fragments	Liquid
Yoghurt (1·5 % fat)	136	15	4·1, whey/casein	Y	Native MFG or homogenised milk fat droplets/potential MFGM fragments	Gel/viscoelastic
Butter	15	–	< 1, –	N/Y†	Continuous fat phase (water-in-oil emulsion)/MFGM-residue traces	–

*Values reported as approximate amounts.
†Differs depending on production method used.
Adapted from Thorning *et al.*[40]

bacteria which, during the fermentation process, can produce SCFA and bioactive peptides. These SCFA and bioactive peptides can impact the health promoting potential of the final fermented food products[55]. SCFA have anti-inflammatory properties[56] and have been linked to reduced risk of colon cancer[57], while the most studied mechanism of bioactive peptides is their anti-hypertensive action, exhibited by the inhibition of the angiotensin-I-converting enzyme which regulates blood pressure[58]. The overall nutrient structure of dairy foods, and the levels of these nutrients within, are impacted by the various processing steps (from milk to food product) and these differences may explain the different health outcomes associated with consumption[38].

Traditional v newer risk markers of CVD

As the research linking SFA content to CVD risk becomes more nuanced, so too do the biological markers of CVD risk. Traditionally, epidemiological studies have focused on reduction of plasma cholesterol levels as clinically relevant markers of reduced CVD risk[59]. It is evident that elevated LDL-C levels play a role in the development of CVD, and causality can be determined[60]. However individuals with LDL-C levels within the normal range can also develop atherosclerosis and CVD[61]. This variation in risk is thought to be due to the heterogeneity of these LDL particles with regards to their size, density and chemical composition[62]. Higher concentration of small, dense LDL-P is associated with an increased risk of CVD, independent of overall LDL-C levels[63]. These small LDL particles are considered to be more pro-atherogenic than large LDL particles due to their decreased affinity for the LDL receptor resulting in a prolonged retention time in the circulation. They can more easily enter and bind to the arterial wall, and are more susceptible to oxidation, which may enhance the uptake by macrophages[64,65]. Dreon et al. demonstrated a correlation between changes in dietary saturated fat and changes in concentration of the larger, more buoyant LDL particles, suggesting that the increases in LDL-C from saturated fat (especially C14:0 and C16:0) were owing to increases in the larger, less atherogenic particles[66]. High-carbohydrate diets, which are associated with lower LDL-C, exhibit a positive correlation with pro-atherogenic small dense LDL-P in RCT[67–69]. One such study by Krauss et al., looked at a group of 178 mildly obese and overweight men that consumed a 26, 39 or 54 % kcal from carbohydrate diet with 7–9 % energy intake as SFA (low-SFA diet) and one group that consumed a 26 % carbohydrate diet and 15 % energy intake as SFA (high-SFA diet) for 3 weeks. They found a linear relationship of increased carbohydrate intake with increased prevalence of small LDL particles. Those on the 26 % carbohydrate, low-SFA diet had reduced TG, ApoB, small LDL particles, and total HDL cholesterol compared to those on a 54 % carbohydrate, low-SFA diet. Those on the 26 % carbohydrate diet with high-SFA exhibited increased concentrations of medium- and large-sized LDL particles[70]. Therefore, changes in both total LDL-C and LDL particle size can result from dietary change and must also be considered in the study of diet and CVD.

LDL-C levels, traditionally used within epidemiological studies examining the link between diet and disease, do not reflect levels of different LDL particle (LDL-P) sizes. Since many dietary recommendations focus solely on a reduction of total fat, or, saturated fat as a means of reducing CVD risk[4], this may result in an overestimation of the beneficial effects of SFA reduction in such studies, by reliance on this change in LDL-C levels alone[5].

In the context of dairy fat and cheese, a study conducted by Raziani et al. in 2018 investigated the effects of full fat *v* reduced fat cheese on LDL particle size distribution, using NMR spectroscopy. They found that overall, LDL particle size distribution was not altered by full fat cheese when compared to reduced fat cheese. A recent, exploratory analysis of biological samples from an earlier study showing reductions in LDL-C following 6 weeks' consumption of cheese *v.* reduced fat cheese *v.* butter[39] further investigated the role of the food matrix on lipoprotein particle size distribution[71]. Results suggested a transition from small pro-atherogenic particles toward larger, more buoyant LDL particles following 6-weeks of

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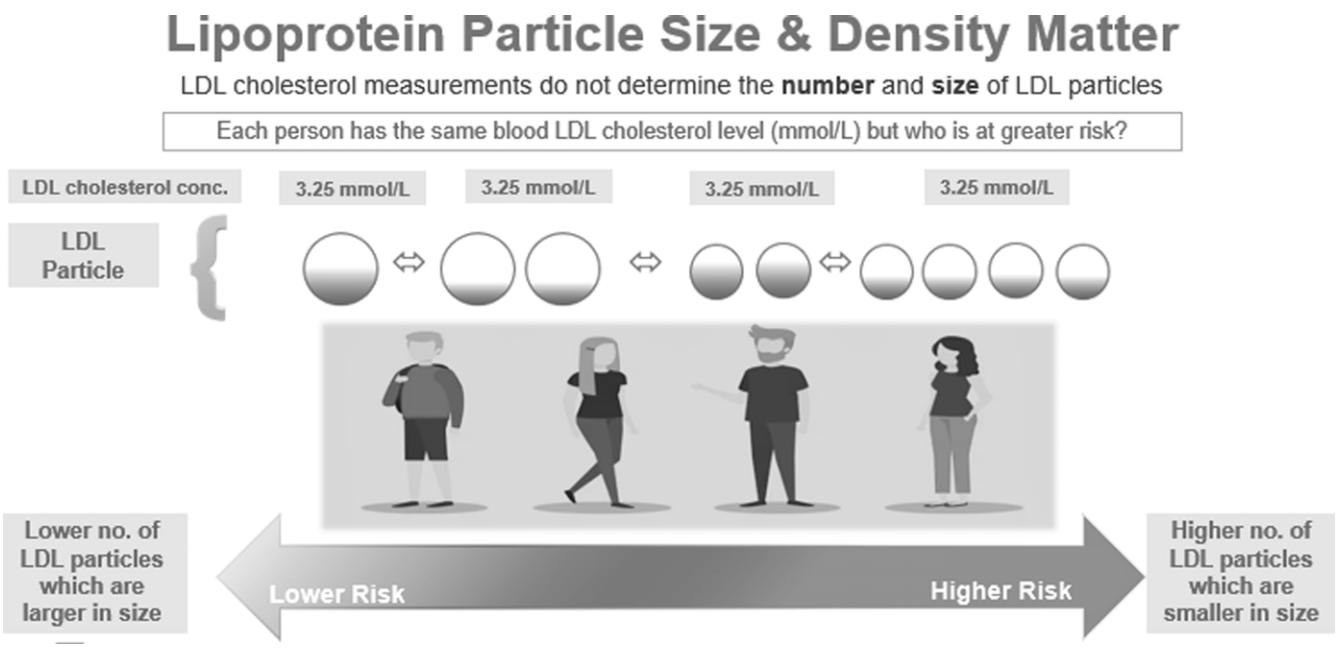

Fig. 1 Individuals with the same LDL cholesterol concentration (mmol/l) can differ in terms of their CVD risk. The risk scale, ranging from lower risk (left side of scale) to higher risk (right side of scale) shows the variation between individuals in terms of their CVD risk when considering the number and size of LDL particles, i.e. those with the lower number of LDL particles, larger in size are lower risk than those with the higher number of LDL particles, smaller in size.

dairy fat consumption (approx. 42 g/d). However, despite the fact that the changes in serum cholesterol levels were influenced by the food matrix, similar changes in LDL particle size were seen for the cheese, butter, and the reduced fat cheese groups[71]. This indicated that there was a dominant role for the nutritional composition within the matrix in driving changes in LDL particle size, over the food matrix effect.

The lipoprotein balance between LDL and HDL particles has traditionally been assessed through measurement of their cholesterol content (LDL-C and HDL-C) as opposed to the number of particles[72]. Distinction between these is important, as the two are not equivalent; for example, two individuals could have the same LDL-C levels but have differing numbers of LDL particles and as a result, a different CVD risk (Fig. 1), i.e. the individual with the higher number of LDL particles would be at increased risk as this would suggest a higher number of small dense particles[73]. Analysis of LDL particle size should therefore be considered as a cornerstone biomarker within nutritional intervention studies for assessment of changes in CVD risk[6].

Emerging nutrition modifiable biomarkers of CVD risk – HDL function and composition

While the causal link between LDL-C and CVD events has been well documented – the role of HDL-C in disease pathophysiology remains more controversial[74]. Increased levels of HDL-C are traditionally associated with reduced CVD risk[75,76] but raising HDL-C levels pharmacologically has not significantly impacted disease outcome[77] and similarly genetically defined high-HDL-C is not associated with reduced outcomes[78]. However, low HDL-C remains a major risk factor associated with the metabolic syndrome[79] and appears, in part, to be driven by an elevation in carbohydrate consumption[80]. In more recent years there has been increasing evidence that measurement of the function of HDL particles (cholesterol efflux capacity (CEC)) is a better approach to assess CVD risk than measurement of static levels of HDL-C[81]. HDL particles play a critical role in reverse cholesterol transport by stimulating the efflux of cholesterol from peripheral cells, including lipid laden macrophages in atherosclerotic lesions, and delivering acquired lipid back to the liver for excretion in the bile and the faeces[82,83]. A reduction in HDL-CEC is evident in acute inflammatory settings, independent of changes in HDL-C levels[84] further demonstrating how measures of HDL-C fail to capture the functional properties of the particles. Another important determinant of HDL function is the size of the particles – small HDL-P can mediate CEC via ABCA1-dependent pathways[85] while larger HDL-P mediate CEC via ABCG1/SR-BI dependent pathway[86] and in general have a larger capacity to store acquired lipid. Changes in HDL-P size in response to a dietary intervention, may therefore modulate the particle's cellular interactions and functional properties independent of changes in HDL-C. Finally, another key consideration on HDL-P is their composition. The HDL proteome in particular has long been considered a potentially key biomarker of CVD risk[87] that to date has not been exploited to its full potential. The HDL proteome is profoundly modulated in patients with CVD and with end-stage kidney disease, with increased

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association of pro-inflammatory proteins and reductions in anti-inflammatory proteins evident on the particles in the diseased state[88–90]. O'Reilly et al., have further demonstrated that the HDL proteome is remarkably sensitive to dietary fat composition within obesogenic diets in preclinical models[84]. Increased association of pro-inflammatory proteins and reductions in anti-inflammatory proteins on HDL particles was evident in mice fed an SFA-enriched high-fat diet relative to mice consuming a MUFA-enriched high-fat diet[84]. Both of these high-fat diets exerted similar increases in HDL-C levels again demonstrating how measurements of HDL-C fail to capture important information on the quality of the particles. Importantly the HDL proteome can mirror metabolic disturbances within the liver, acting as a novel systemic biomarker of hepatic dysmetabolism and chronic low-grade inflammation but within an easily accessible blood matrix[91]. The HDL proteome is therefore an exciting future 'immunometabolic' biomarker for the nutrition field that may sensitively detect changes in hepatic metabolism and low-grade inflammation, and ultimately identify patients at high-risk of CVD. Importantly, reversal of these adverse changes in particle composition in response to dietary interventions, independent of changes in HDL-C, may provide important mechanistic insights on the health benefits of novel functional foods.

Conclusion

Current evidence still suggests that saturated fat intake be kept as low as possible, and ideally < 10 % of total energy intake. However, as the evidence base grows in this area, these guidelines may need to be revisited.

When considering the link between saturated fat and CVD risk, more recent work indicates that it is important to consider this risk within the context of individual foods (food matrix) using more accurate risk markers (LDL particle size and HDL functionality/composition).

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Conflict of Interest

There are no conflicts of interest.

Authorship

S.D completed the review, E.L.F, E.R.G and F.C.M advised and critically evaluated. All authors read and approved the final manuscript.

References

1. World Health Organisation (2017) Cardiovascular Diseases. https://www.who.int/health-topics/cardiovascular-diseases/#tab=tab_1 (accessed 29 April 2021).
2. Briggs MA, Petersen KS & Kris-Etherton PM (2017) Saturated fatty acids and cardiovascular disease: replacements for saturated fat to reduce cardiovascular risk. *Healthcare (Basel)* **5**, 29.
3. Mensink RP (2016) *Effects of Saturated Fatty Acids on Serum Lipids and Lipoproteins: A Systematic Review and Regression Analysis*. Geneva: WHO.
4. EFSA (2017) Dietary reference values for nutrients summary report. *EFSA Supporting Publ* **14**, 98.
5. Astrup A, Magkos F, Bier DM *et al.* (2020) Saturated fats and health: a reassessment and proposal for food-based recommendations: JACC State-of-the-Art Review. *J Am Coll Cardiol* **76**, 844–857.
6. Cromwell WC, Otvos JD, Keyes MJ *et al.* (2007) LDL particle number and risk of future cardiovascular disease in the Framingham Offspring Study – implications for LDL management. *J Clin Lipidol* **1**, 583–592.
7. Li Y, Hruby A, Bernstein AM *et al.* (2015) Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: a prospective cohort study. *J Am Coll Cardiol* **66**, 1538–1548.
8. Ley SJ, Metcalf PA, Scragg RK *et al.* (2004) Long-term effects of a reduced fat diet intervention on cardiovascular disease risk factors in individuals with glucose intolerance. *Diabetes Res Clin Pract* **63**, 103–112.
9. Siri-Tarino PW, Sun Q, Hu FB *et al.* (2010) Saturated fatty acids and risk of coronary heart disease: modulation by replacement nutrients. *Curr Atheroscler Rep* **12**, 384–390.
10. SACN (2019) Saturated fats and health Public Health England. https://assets.publishing.service.gov.uk/media/5d1f88af40f0b609dba90ddc/SACN_report_on_saturated_fat_and_health.pdf (accessed January 2021).
11. Hooper L, Martin N, Jimoh OF *et al.* (2020) Reduction in saturated fat intake for cardiovascular disease. *Cochrane Database Syst Rev* issue 8, CD011737.
12. Lichtenstein AH, Kennedy E, Barrier P *et al.* (1998) Dietary fat consumption and health. *Nutr Rev* **56**, 3–19.
13. Burdge GC & Calder PC (2015) Introduction to fatty acids and lipids. *World Rev Nutr Diet* **112**, 1–16.
14. Chow CK (2007) *Fatty Acids in Foods and their Health Implications*, 3rd ed. London: CRC Press.
15. Brown HA & Marnett LJ (2011) Introduction to lipid biochemistry, metabolism, and signaling. *Chem Rev* **111**, 5817–5820.
16. Calder PC (2015) Functional roles of fatty acids and their effects on human health. *J Parenteral Enteral Nutr* **39**, 18S–32S.
17. Radzikowska U, Rinaldi AO, Celebi Sozener Z *et al.* (2019) The influence of dietary fatty acids on immune responses. *Nutrients* **11**, 2990.
18. Ratnayake WM & Galli C (2009) Fat and fatty acid terminology, methods of analysis and fat digestion and

https://doi.org/10.1017/S0029665124000132 Published online by Cambridge University Press

metabolism: a background review paper. *Ann Nutr Metab* **55**, 8–43.
19. Lawrence GD (2013) Dietary fats and health: dietary recommendations in the context of scientific evidence. *Adv Nutr* **4**, 294–302.
20. Keys A (1970) Coronary heart disease in seven countries. *Circulation* **41**, 186–195.
21. Hu FB, Stampfer MJ, Manson JE *et al.* (1997) Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* **337**, 1491–1499.
22. Appel LJ, Champagne CM, Harsha DW *et al.* (2003) Effects of comprehensive lifestyle modification on blood pressure control: main results of the PREMIER clinical trial. *JAMA* **289**, 2083–2093.
23. Astrup A, Bertram HCS, Bonjour J-P *et al.* (2019) WHO draft guidelines on dietary saturated and trans fatty acids: time for a new approach? *BMJ* **366**, l4137.
24. de Souza RJ, Mente A, Maroleanu A *et al.* (2015) Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ* **351**, h3978.
25. Ho FK, Gray SR, Welsh P *et al.* (2020) Associations of fat and carbohydrate intake with cardiovascular disease and mortality: prospective cohort study of UK Biobank participants. *BMJ* **368**, m688.
26. Kang ZQ, Yang Y & Xiao B (2020) Dietary saturated fat intake and risk of stroke: systematic review and dose-response meta-analysis of prospective cohort studies. *Nutr Metab Cardiovasc Dis* **30**, 179–189.
27. Li Z, Lei H, Jiang H *et al.* (2022) Saturated fatty acid biomarkers and risk of cardiometabolic diseases: a meta-analysis of prospective studies. *Front Nutr* **9**, 963471.
28. Zhu Y, Bo Y & Liu Y (2019) Dietary total fat, fatty acids intake, and risk of cardiovascular disease: a dose-response meta-analysis of cohort studies. *Lipids Health Dis* **18**, 91.
29. Mente A, Dehghan M, Rangarajan S *et al.* (2017) Association of dietary nutrients with blood lipids and blood pressure in 18 countries: a cross-sectional analysis from the PURE study. *Lancet Diabetes Endocrinol* **5**, 774–787.
30. Micha R & Mozaffarian D (2010) Saturated fat and cardiometabolic risk factors, coronary heart disease, stroke, and diabetes: a fresh look at the evidence. *Lipids* **45**, 893–905.
31. Dehghan M, Mente A, Zhang X *et al.* (2017) Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. *Lancet* **390**, 2050–2062.
32. Fretts AM, Mozaffarian D, Siscovick DS *et al.* (2014) Plasma phospholipid saturated fatty acids and incident atrial fibrillation: the Cardiovascular Health Study. *J Am Heart Assoc* **3**, e000889.
33. Kris-Etherton PM & Yu S (1997) Individual fatty acid effects on plasma lipids and lipoproteins: human studies. *Am J Clin Nutr* **65**, 1628S–1644S.
34. Perna M & Hewlings S (2022) Saturated fatty acid chain length and risk of cardiovascular disease: a systematic review. *Nutrients* **15**, 30.
35. Praagman J, de Jonge EA, Kiefte-de Jong JC *et al.* (2016) Dietary saturated fatty acids and coronary heart disease risk in a Dutch middle-aged and elderly population. *Arterioscler Thromb Vasc Biol* **36**, 2011–2018.
36. Praagman J, Vissers LET, Mulligan AA *et al.* (2019) Consumption of individual saturated fatty acids and the risk of myocardial infarction in a UK and a Danish cohort. *Int J Cardiol* **279**, 18–26.
37. Zong G, Li Y, Wanders AJ *et al.* (2016) Intake of individual saturated fatty acids and risk of coronary heart disease in US men and women: two prospective longitudinal cohort studies. *BMJ* **355**, i5796.
38. Timon CM, O'Connor A, Bhargava N *et al.* (2020) Dairy consumption and metabolic health. *Nutrients* **12**, 3040.
39. Feeney EL, Barron R, Dible V *et al.* (2018) Dairy matrix effects: response to consumption of dairy fat differs when eaten within the cheese matrix-a randomized controlled trial. *Am J Clin Nutr* **108**, 667–674.
40. Thorning TK, Bertram HC, Bonjour JP *et al.* (2017) Whole dairy matrix or single nutrients in assessment of health effects: current evidence and knowledge gaps. *Am J Clin Nutr* **105**, 1033–1045.
41. Astrup A, Geiker NRW & Magkos F (2019) Effects of full-fat and fermented dairy products on cardiometabolic disease: food is more than the sum of its parts. *Adv Nutr* **10**, 924S–930S.
42. Vissers LET, Rijksen J, Boer JMA *et al.* (2019) Fatty acids from dairy and meat and their association with risk of coronary heart disease. *Eur J Nutr* **58**, 2639–2647.
43. Feeney EL, Nugent AP, Mc Nulty B *et al.* (2016) An overview of the contribution of dairy and cheese intakes to nutrient intakes in the Irish diet: results from the National Adult Nutrition Survey. *Br J Nutr* **115**, 709–717.
44. Feeney EL & McKinley MC (2020) The dairy food matrix: what it is and what it does. In *Milk and Dairy Foods Their Functionality in Human Health and Disease*, pp. 205–225 [I Givens, editor]. Cambridge, MA: Academic Press.
45. de Goede J, Geleijnse JM, Ding EL *et al.* (2015) Effect of cheese consumption on blood lipids: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev* **73**, 259–275.
46. Michas G, Micha R & Zampelas A (2014) Dietary fats and cardiovascular disease: putting together the pieces of a complicated puzzle. *Atherosclerosis* **234**, 320–328.
47. Yuan M, Singer MR, Pickering RT *et al.* (2022) Saturated fat from dairy sources is associated with lower cardiometabolic risk in the Framingham Offspring Study. *Am J Clin Nutr* **116**, 1682–1692.
48. Chen Z, Ahmed M, Ha V *et al.* (2022) Dairy product consumption and cardiovascular health: a systematic review and meta-analysis of prospective cohort studies. *Adv Nutr* **13**, 439–454.
49. Drouin-Chartier JP, Brassard D, Tessier-Grenier M *et al.* (2016) Systematic review of the association between dairy product consumption and risk of cardiovascular-related clinical outcomes. *Adv Nutr* **7**, 1026–1040.
50. Brassard D, Tessier-Grenier M, Allaire J *et al.* (2017) Comparison of the impact of SFAs from cheese and butter on cardiometabolic risk factors: a randomized controlled trial. *Am J Clin Nutr* **105**, 800–809.
51. Nestel PJ, Chronopulos A & Cehun M (2005) Dairy fat in cheese raises LDL cholesterol less than that in butter in mildly hypercholesterolaemic subjects. *Eur J Clin Nutr* **59**, 1059–1063.
52. Hjerpsted J, Leedo E & Tholstrup T (2011) Cheese intake in large amounts lowers LDL-cholesterol concentrations compared with butter intake of equal fat content. *Am J Clin Nutr* **94**, 1479–1484.
53. Weaver CM (2021) Dairy matrix: is the whole greater than the sum of the parts? *Nutr Rev* **79**, 4–15.
54. Dewettinck K, Rombaut R, Thienpont N *et al.* (2008) Nutritional and technological aspects of milk fat globule membrane material. *Int Dairy J* **18**, 436–457.

https://doi.org/10.1017/S0029665124000132 Published online by Cambridge University Press

55. Leeuwendaal NK, Stanton C, O'Toole PW *et al.* (2022) Fermented foods, health and the gut microbiome. *Nutrients* **14**, 1527.
56. Smith PM, Howitt MR, Panikov N *et al.* (2013) The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* **341**, 569–573.
57. Morrison DJ, Mackay WG, Edwards CA *et al.* (2006) Butyrate production from oligofructose fermentation by the human faecal flora: what is the contribution of extracellular acetate and lactate? *Br J Nutr* **96**, 570–577.
58. Fernandez M, Hudson JA, Korpela R *et al.* (2015) Impact on human health of microorganisms present in fermented dairy products: an overview. *Biomed Res Int* **2015**, 412714.
59. Scandinavian Simvastatin Survival Study Group (1994) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* **344**, 1383–1389.
60. Ference BA, Ginsberg HN, Graham I *et al.* (2017) Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J* **38**, 2459–2472.
61. Raziani F, Ebrahimi P, Engelsen SB *et al.* (2018) Consumption of regular-fat *v.* reduced-fat cheese reveals gender-specific changes in LDL particle size – a randomized controlled trial. *Nutr Metab (Lond)* **15**, 61.
62. Lakshmy R, Dorairaj P, Tarik M *et al.* (2012) LDL particle heterogeneity, and its association with other established cardiovascular risk factors in a young Indian industrial population. *Heart Asia* **4**, 141–145.
63. Lamarche B, Lemieux I & Després JP (1999) The small, dense LDL phenotype and the risk of coronary heart disease: epidemiology, patho-physiology and therapeutic aspects. *Diabetes Metab* **25**, 199–211.
64. Vekic J, Zeljkovic A, Cicero AFG *et al.* (2022) Atherosclerosis development and progression: the role of atherogenic small, dense LDL. *Medicina (Kaunas)* **58**, 299.
65. Feingold KR (2000–2023) *Introduction to Lipids and Lipoproteins*. South Dartmouth, MA: MDText.com, Inc.
66. Dreon DM, Fernstrom HA, Campos H *et al.* (1998) Change in dietary saturated fat intake is correlated with change in mass of large low-density-lipoprotein particles in men. *Am J Clin Nutr* **67**, 828–836.
67. Krauss RM & Dreon DM (1995) Low-density-lipoprotein subclasses and response to low-fat diet in healthy men. *Am J Clin Nutr* **62**, 478S–487S.
68. Dreon DM, Fernstrom HA, Williams PT *et al.* (1999) A very low-fat diet is not associated with improved lipoprotein profiles in men with a predominance of large, low-density lipoproteins. *Am J Clin Nutr* **69**, 411–418.
69. Faghihnia N, Tsimikas S, Miller ER *et al.* (2010) Changes in lipoprotein(a), oxidized phospholipids, and LDL subclasses with a low-fat high-carbohydrate diet. *J Lipid Res* **51**, 3324–3330.
70. Krauss RM, Blanche PJ, Rawlings RS *et al.* (2006) Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. *Am J Clin Nutr* **83**, 1025–1031; quiz 1205.
71. Dunne S, McGillicuddy FC, Gibney ER *et al.* (2023) Role of food matrix in modulating dairy fat induced changes in lipoprotein particle size distribution in a human intervention. *Am J Clin Nutr* **117**, 111–120.
72. Jeyarajah EJ, Cromwell WC & Otvos JD (2006) Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. *Clin Lab Med* **26**, 847–870.
73. Otvos JD (2002) Why cholesterol measurements may be misleading about lipoprotein levels and cardiovascular disease risk – clinical implications of lipoprotein quanitification using NMR spectroscopy *J Lab Med* **26**, 544–550.
74. Asztalos BF, Horvath KV & Schaefer EJ (2018) High-density lipoprotein particles, cell-cholesterol efflux, and coronary heart disease risk. *Arterioscler Thromb Vasc Biol* **38**, 2007–2015.
75. Ballantyne CM, Herd JA, Ferlic LL *et al.* (1999) Influence of low HDL on progression of coronary artery disease and response to Fluvastatin therapy. *Circulation* **99**, 736–743.
76. Nicholls SJ, Tuzcu EM, Sipahi I *et al.* (2007) Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* **297**, 499–508.
77. Tall AR & Rader DJ (2018) Trials and tribulations of CETP Inhibitors. *Circ Res* **122**, 106–112.
78. Wilkins JT, Ning H, Stone NJ *et al.* (2014) Coronary heart disease risks associated with high levels of HDL cholesterol. *J Am Heart Assoc* **3**, e000519.
79. Kaur N, Pandey A, Negi H *et al.* (2014) Effect of HDL-raising drugs on cardiovascular outcomes: a systematic review and meta-regression. *PLoS One* **9**, e94585.
80. Shin WK, Shin S, Lee Jk *et al.* (2020) Carbohydrate intake and hyperlipidemia among population with high-carbohydrate diets: the Health Examinees Gem Study. *Mol Nutr Food Res* **65**, 2000379.
81. Khera AV, Cuchel M, de la Llera-Moya M *et al.* (2011) Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med* **364**, 127–135.
82. Vyletelova V, Novakova M & Paskova L (2022) Alterations of HDL's to piHDL's proteome in patients with chronic inflammatory diseases, and HDL-Targeted therapies. *Pharmaceuticals (Basel)* **15**, 1278.
83. Rader DJ & Hovingh GK (2014) HDL and cardiovascular disease. *Lancet* **384**, 618–625.
84. O'Reilly M, Dillon E, Guo W *et al.* (2016) High-density lipoprotein proteomic composition, and not efflux capacity, reflects differential modulation of reverse cholesterol transport by saturated and monounsaturated fat diets. *Circulation* **133**, 1838–1850.
85. Fazio S & Pamir N (2016) HDL particle size and functional heterogeneity. *Circ Res* **119**, 704–707.
86. Rubinow KB, Vaisar T, Chao JH *et al.* (2018) Sex steroids mediate discrete effects on HDL cholesterol efflux capacity and particle concentration in healthy men. *J Clin Lipidol* **12**, 1072–1082.
87. Reilly MP & Tall AR (2007) HDL proteomics: pot of gold or Pandora's box? *J Clin Invest* **117**, 595–598.
88. Bonizzi A, Piuri G, Corsi F *et al.* (2021) HDL dysfunctionality: clinical relevance of quality rather than quantity. *Biomedicines* **9**, 729.
89. Tolle M, Huang T, Schuchardt M *et al.* (2012) High-density lipoprotein loses its anti-inflammatory capacity by accumulation of pro-inflammatory-serum amyloid A. *Cardiovasc Res* **94**, 154–162.
90. Shao B, Mathew AV, Thornock C *et al.* (2021) Altered HDL proteome predicts incident CVD in chronic kidney disease patients. *J Lipid Res* **62**, 100135.
91. Kajani S, Curley S, O'Reilly ME *et al.* (2022) Sodium salicylate rewires hepatic metabolic pathways in obesity and attenuates IL-1beta secretion from adipose tissue: the implications for obesity-impaired reverse cholesterol transport. *Mol Metab* **56**, 101425.

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