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Review article

Circulating ceramides as biomarkers of cardiovascular disease: Evidence from phenotypic and genomic studies

Kathryn A. McGurk [a,b,1], Bernard D. Keavney [a,c], Anna Nicolaou [b,d,*]

[a] Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, UK
[b] Laboratory for Lipidomics and Lipid Research, Division of Pharmacy and Optometry, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, UK
[c] Manchester Heart Centre, Manchester University NHS Foundation Trust, UK
[d] Lydia Becker Institute of Immunology and Inflammation, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK

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ABSTRACT

There is a need for new biomarkers of atherosclerotic cardiovascular disease (ACVD), the main cause of death globally. Ceramides, a class of potent bioactive lipid mediators, have signalling roles in apoptosis, cellular stress and inflammation. Recent studies have highlighted circulating ceramides as novel biomarkers of coronary artery disease, type-2 diabetes and insulin resistance. Ceramides are highly regulated by enzymatic reactions throughout the body in terms of their activity and metabolism, including production, degradation and transport. The genetic studies that have been completed to date on the main ceramide species found in circulation are described, highlighting the importance of DNA variants in genes involved in ceramide biosynthesis as key influencers of heritable, circulating ceramide levels. We also review studies of disease associations with ceramides and discuss mechanistic insights deriving from recent genomic studies. The signalling activities of ceramides in vascular inflammation and apoptosis, associations between circulating ceramides and coronary artery disease risk, type-2 diabetes and insulin resistance, and the potential importance of ceramides with regard to ACVD risk factors, such as blood pressure, lipoproteins and lifestyle factors, are also discussed.

1. Ceramides as potential biomarkers of cardiovascular disease

Traditional biomarkers of atherosclerotic cardiovascular disease (ACVD), such as blood levels of lipoproteins, fail to identify all patients at high risk of cardiovascular events (reviewed in Ref. [1]). There is an on-going need for the discovery of novel biomarkers to improve our understanding of causality, as well as the prediction, prevention and treatment, of ACVD risk.

Ceramides are a class of bioactive lipids which are present during vascular inflammation [2–6]. Their signalling properties mainly involve the regulation of apoptosis [7]. Ceramides are found in lipoprotein complexes [8,9] and are also produced by platelets [10], potentially linking ceramide signalling to atherosclerosis progression and pathology. There is a growing body of evidence that circulating ceramides may predict ACVD risk, and may potentially be more predictive than LDL cholesterol [9,11–15]. This review describes the potential value of circulating ceramide species in ACVD-risk and discusses novel insights from recent phenotypic and genetic studies. A number of *in vitro* experiments supporting clinical findings have been published (e.g. Refs. [7,16,17]) but their detailed examination is outside the scope of this review.

2. Ceramide biochemistry and biology

Ceramides are sphingolipids, a class of bioactive lipids with key roles in cell signalling, proliferation, differentiation, senescence, adhesion, migration, inflammation and angiogenesis [16,18]. They are produced *de novo* but also recycled and stored as complex sphingolipids through well-controlled and highly conserved reversible enzyme reactions, such as the conversion to sphingosine, sphingomyelin, and other sphingolipids such as hexosylceramides (Fig. 1A) [18,19].

The initiation step of ceramide biosynthesis is controlled by the

* Corresponding author. Division of Pharmacy and Optometry, Stopford Building, Oxford Road, University of Manchester, Manchester, M13 9PL, UK.
E-mail address: anna.nicolaou@manchester.ac.uk (A. Nicolaou).
[1] Present address: National Heart and Lung Institute, Imperial College London, London, UK.

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enzyme serine palmitoyl transferase (SPTLC) that catalyses the condensation of palmitate and serine to form the sphingoid base dihydrosphingosine (C18DS); this is also the rate limiting step of the pathway [16]. The enzyme ceramide synthase (CERS) adds acyl chains of various lengths to form dihydroceramides (CER[NDS]), which are desaturated by dihydroceramide desaturase-1 (DEGS1) to produce a wide range of ceramides (CER[NS]), differing by carbon chain length. Isoforms of the genes of these enzymes (i.e. *SPTLC1-3, CERS1-6*) have different substrate specificity and tissue expression profiles, facilitating the formation of hundreds of ceramide species [20,21]. Degradation of ceramides is reversible to and from sphingosine; ceramidases (*ACER1-3*) catalyse the degradation of ceramides to sphingosine and sphingosine-1 phosphate, with further irreversible reactions forming hexadecanal and phosphoethanolamine that can then be recycled to biosynthesise other lipids [22].

Ceramide biosynthesis is induced by a broad range of stimuli, hormonal signals (e.g. progesterone, nerve growth factor), inflammatory stimuli (tumour necrosis factor, interferons, endotoxins, LPS), chemotherapeutics, ionising radiation, heat, alterations in the microbiome, inducers of cell activities (apoptosis, differentiation, and growth suppression, e.g. Fas ligand and CD28) [16,18,19,23–26].

Ceramides are produced by various cells and tissues, including the liver [27,28]. It is likely that the levels of ceramide species in blood are due to a contribution from several tissue origins. The most abundant blood ceramides currently associated with ACVD risk are derivatives of the C18-sphingoid bases sphingosine [S] and dihydrosphingosine [DS] [29].

The nomenclature of ceramides has evolved as the field expands. The notation proposed by Masakawa et al. (2008) describes more than 12 ceramides classes discovered to date [21]. The majority of circulating ceramides belong to the CER[NS] class of species containing a non-hydroxy fatty acid [N] attached to sphingosine [S]; for example, a ceramide with a 24-carbon non-hydroxy fatty acid and a 18-carbon sphingosine is denoted as CER[N(24)S(18)] (Fig. 1B). This species is also denoted as Cer (d18:1/24:0) and C24-Cer in literature. Here we adhere to the CER[NS] nomenclature.

3. Ceramides as putative cardiovascular disease risk factors

3.1. Apoptosis and inflammation

Ceramides have been well studied for their roles in apoptosis [7], a key process in atherosclerotic plaque biology [30]. Ceramide species initiate apoptosis by signalling from the plasma membrane at pro-apoptotic receptors [31] or directly at the mitochondrial outer membrane in the cell, causing permeabilisation of the mitochondrial membrane [31–33]. Ceramides regulate the many components of cell survival including initiation and mediation of apoptosis and growth arrest, inhibition of anti-apoptotic mediators [19], and cell differentiation [8,18,34]. Caspases, key enzymes of the apoptotic pathway, regulate the production of ceramide species and are themselves in turn targets of ceramide action [19]. Apoptosis has been implicated in the many aspects of ACVD [35–37]. For example, cardiomyocytes undergoing apoptosis have been found in tissues from myocardial infarction, diabetic cardiomyopathy, and heart failure patients [37]. A synthetic analogue of the ceramide CER[N(16)S(18)] has been shown to trigger apoptosis of cardiomyocytes during ischemia and reperfusion in rats [38].

Ceramides have also been implicated in inflammation and vasoconstriction. Increases in intracellular ceramide levels signal the NLRP3 inflammasome to induce apoptosis in macrophages and adipose tissue

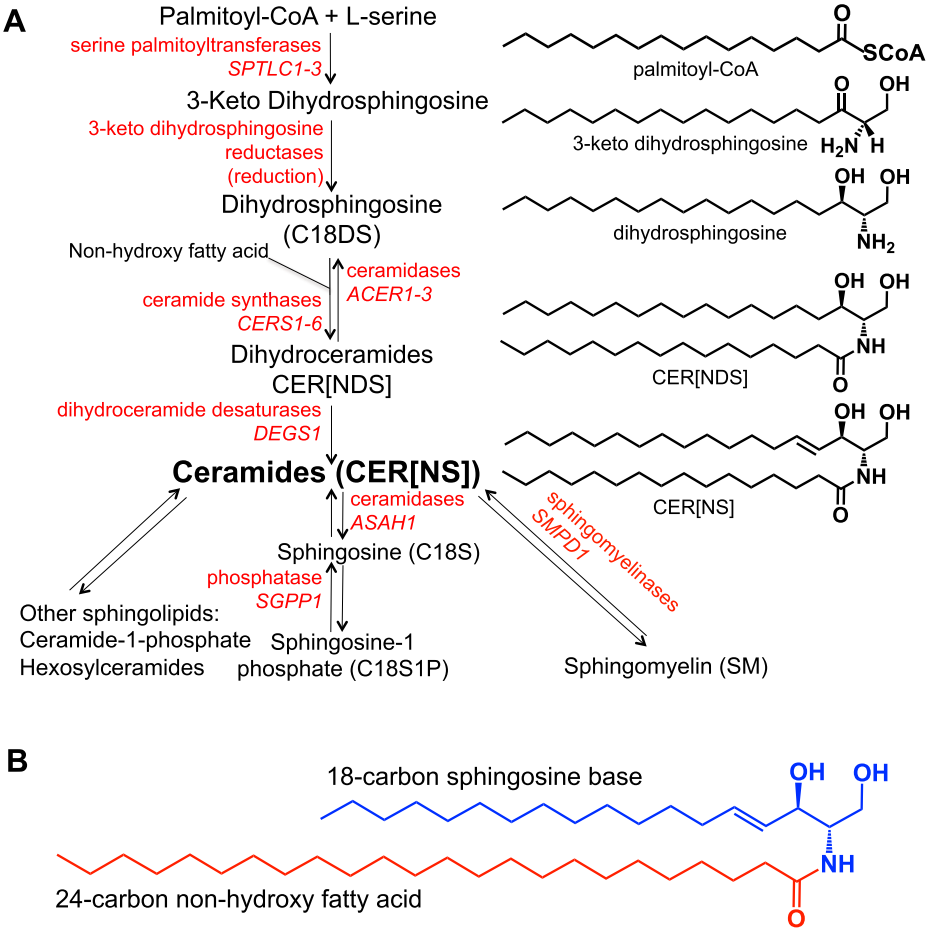

Fig. 1. The ceramide biosynthetic pathway with example structures.
(A) The *de novo* biosynthetic pathway of ceramides (CER[NS]) is depicted. In the endoplasmic reticulum, palmitoyl-CoA and L-serine undergo condensation by serine palmitoyltransferase (SPTLC) to produce 3-keto-dihydrosphingosine, which has a short half-life. It is reduced by a reductase enzyme (3-keto-dihydrosphingosine reductase) to form dihydrosphingosine (C18DS), a sphingoid base. This base is n-acylated, incorporating a fatty acid side chain by ceramide synthase enzymes (CERS) to produce dihydroceramides (CER[NDS]), the precursors of CER[NS] species. CER[NDS] are desaturated to CER[NS] by incorporation of a 4,5-trans-double bond by desaturase enzymes (dihydroceramide desaturase; *DEGS1*). There are many reversible reactions that can be initiated from CER[NS] species. CER[NS] can be recycled to other sphingolipid mediators (for example phosphorylated to ceramide-1-phosphate), stored in the membrane as sphingomyelin (SM), or degraded through reversible reactions to sphingosine (C18S). (B) CER[NS] class of ceramide species contain a non-hydroxy fatty acid [N] attached to sphingosine [S]. The figure depicts CER[N(24)S(18)] species; a ceramide with a 24-carbon non-hydroxy fatty acid attached to an 18-carbon sphingosine. In literature, a different nomenclature describes this species also as Cer (d18:1/24:0), to represent the double bonds in the structure ([18 carbon sphingoid base: 1 double bond]/[24 carbon fatty acid: 0 double bond]), or C24-Cer, which assumes that the ceramide has an 18-carbon sphingosine.

[6]. In 33 coronary artery disease patients, levels of serum ceramides (e.g. CER[N(23)S(18)] and CER[N(24:1)S(18)]) correlated with interleukin-6 concentration (IL-6) [2]. IL-6 has been implicated in inflammation, accelerating atherosclerosis risk in rheumatoid arthritis patients [39], and adiponectin is an anti-diabetic and cardio-protective protein hormone that has been shown to decrease ceramide levels in obesity models [4] to allow for cell survival [5]. In patients with obesity, ceramides have been shown to interact with interleukins [2], as well as TNF-α and adiponectin [3]. The adiponectin receptor in yeast, the PAQR receptor (progestin and adipoQ receptor), has sequence homology to ceramidases (*ACER*) [40], the enzyme which degrades ceramides to sphingosine for cell survival, potentially highlighting interplay between adiponectin and CER[NS] degradation in the regulation of apoptosis.

3.2. Diet, exercise and obesity

Diet does not appear to substantially alter circulating ceramide concentrations. In a study of 200 participants comparing plasma ceramide levels in subjects with low fat diet *versus* control regular-fat diet, ceramide levels did not show any significant differences with the alteration in diet [41]. There was also no effect on plasma ceramide levels in a study of the Mediterranean diet in 980 participants, where their Mediterranean diet was supplemented with olive oil or nuts, or they were on a non-Mediterranean control diet [15]. In a study of 18 participants, total serum ceramides decreased with a diet low in palmitic acid, and high in oleic acid [42]. Palmitic acid is required for *de novo* ceramide biosynthesis and decrease in diet palmitic acid may reduce ceramide production.

Regular exercise has a positive impact on cardiovascular health and decreases cardiovascular risk factors [43], but the impact of circulating ceramide levels on exercise and obesity is currently unclear and requires future studies with more substantial sample sizes. Exercise has been shown to decrease circulatory ceramide levels in a small sample of eight participants [44]. Knockout mice of the ceramide synthase isoforms *CERS5* and *CERS6* were protected from high-fat-diet-induced obesity and glucose intolerance [45–47]. In humans, maternal obesity and a reduction in plasma ceramides in 47 mother-infant dyads lead to long-term decreased levels of plasma ceramides in four-year-old offspring [48].

3.3. Relationship with established lipoprotein biomarkers of ACVD

Ceramides are packed in lipoprotein complexes and are found at higher concentration in LDL than HDL or VLDL [49]. They have been shown to contribute to the retention of LDL in atherosclerotic lesions [50], enhance macrophage uptake of LDL cholesterol [24], and allow for increased transcytosis of LDL across vascular endothelial cells [51] in atherosclerosis progression. Furthermore, oxidised-LDL has been shown to induce the co-localisation of ceramides and sphingomyelin in membrane lipid rafts of cultured human coronary arterial endothelial cells, which is blocked by statins [52].

However, many of the studies exploring the relationship between ceramides and current cardiovascular disease risk markers only depict the sum (total) plasma ceramide concentrations instead of the individual ceramide species measured. For example, total ceramide level associated positively with lipid biomarkers (total cholesterol ($R = 0.65$, $p < 0.01$), triglycerides ($R = 0.44$, $p < 0.01$), and phospholipids ($R = 0.66$, $p < 0.01$), in one study of 1000 Japanese participants [53]. Another study of 15 participants identified a significant relationship between total plasma ceramides and VLDL apoB-100 fractional catabolic rate ($r = -0.67$) [54]. These positive associations between total circulating ceramide levels and current clinical biomarkers of ACVD is encouraging, however this relationship could be fully uncovered in the future with the assessment of ceramides as unique entities [55].

3.4. Age

Plasma ceramides were measured in 992 participants in a longitudinal study of aging, which showed increased plasma ceramide concentrations with age [56]. Another study of 164 participants also identified this positive association between circulating ceramide levels and age [57], as did a study of diabetes in 2145 participants [58]. This association with age has also been identified in rat liver [59], mouse plasma, and aortic tissue (ApoE knockouts) [60], and sheep blood vessels [61]. Of note, *Drosophila melanogaster* loss of function of ceramide transport protein (*CERT*) mutants, which cannot transport ceramides to the Golgi for storage, decreased total body ceramide levels, showed premature aging, died earlier than expected, and had increased glucose levels [62].

Telomerases, key enzymes involved in the regulation of cellular aging, are repressed by ceramides through deacetylation of epigenetic factors of the telomerase reverse transcriptase promoter (catalytic unit of telomerase) in human lung adenocarcinoma cells, causing rapid aging [63]. Another study measured total ceramides indirectly via a kinase assay, and found that ceramide levels positively correlated with increased activation of phosphatases and sphingomyelinases in arteries and endothelia of aged rats, and linked ceramides to loss of vasomotor function [64].

3.5. Blood pressure

Positive associations have been found between ceramides and blood pressure or vasoconstriction from both human and animal studies. A number of plasma hexosylceramides were shown to associate with diastolic blood pressure, mean arterial blood pressure [65] and systolic blood pressure [53] in 42 Mexican American families. In spontaneously hypertensive rats (SHR) with increased plasma ceramides by inhibition of ceramide degradation through increased expression of sphingomyelinases (*SMPD1*), endothelium-dependent vasoconstriction and increased blood pressure were identified. This was absent in normotensive Wistar-Kyoto rats [66] and was repeated in human plasma samples from 18 patients with essential hypertension, compared to 18 normotensive controls. In a separate study, inhibiting ceramide *de novo* production in rats on a high fat diet by intervention with myriocin, a SPTLC inhibitor, improved endothelium-dependent vasodilation and reversed atherosclerosis [67]. Other studies have also found that ceramides initiate vasoconstriction in rat and human pulmonary arteries [68] and bovine coronary arteries [69].

3.6. Atherosclerotic cardiovascular disease and associated complications

A number of ceramide species have been recently implicated as novel biomarkers of ACVD risk and associated complications. The associations reported in each of the studies for the individual ceramide species implicated in ACVD risk are summarised in Table 1. These studies highlight CER[N(16)S(18)] as a risk ceramide species by positive association with broad fatal cardiovascular outcomes including coronary artery disease (CAD), major adverse cardiovascular events (MACE), and acute coronary syndrome (ACS). This ceramide is increased in concentration in participants with a fatal outcome, and in participants who have experienced a MACE.

As depicted in the studies summarised in Table 1, the evidence for association of the ceramide species CER[N(24)S(18)] with ACVD describes the ceramide acting in opposition to the other ceramides measured, with respect to ACVD risk. It is identified at lower concentrations in patients than healthy controls, particularly decreased in concentration in the participants with fatal outcome. Thus, it may be a cardio-protective ceramide species.

Ratios between ceramides, of shorter ceramides to CER[N(24)S(18)], were found to have a positive association with fatal outcome in participants experiencing acute coronary syndrome (ACS) [9,11,13,70]. The

Table 1
Ceramide species measured in circulation and their associations with coronary-artery disease (A-D) and type-2 diabetes (E) outcomes [109–111].
(A) Fatal outcome (by hazard or odds ratio)

	[11]	[13]	[13]	[9]	[70]	[109]	[109]	[110]	[111]
Mortalities	258	81	51	Mortality or	Mortality or	Fatal Incident	Fatal Recurrent	200	26
Controls (n)	Stable CAD	Stable CAD	Stable CAD	516	574	Incident MACE	Recurrent MACE	CHF	AMI
N(14)S(18)									NS
N(16)S(18)		Positive	Positive	Positive	Positive	Positive[b]	Positive		Positive
N(18)S(18)		Positive[b]	Positive			Positive[b]	Positive[b]	NM	NS
N(18:1)S(18)									P=0.047
N(20)S(18)					Positive			NM	NS
N(20:4)S(18)									NS
N(22)S(18)								NM	NS
N(22:1)S(18)									NS
N(23)S(18)									NS
N(24)S(18)		NS	Negative[b]	NM	NS	NS	NS	NM	NS
N(24:1)S(18)		Positive	Positive[b]		Positive[b]	NS	Positive		Positive
N(25)S(18)									Positive
N(26)S(18)									NS
N(26:1)S(18)									Positive
N(16)S(18)/ N(24)S(18)	Positive	Positive	Positive	Positive	Positive	NS	NS		
N(18)S(18)/ N(24)S(18)	Positive	Positive	Positive			Positive	NS		
N(20)S(18)/ N(24)S(18)				Positive	Positive				
N(24)S(18)/ N(24:1)S(18)	Negative								
N(24:1)S(18)/ N(24)S(18)		Positive	Positive	Positive	Positive	NS	NS		
Total								Positive	

(B) Fatal outcome (by mean concentration)

Reference	[11]	[13]	[13]	[13]
Mortalities (n)	258	81	51	80
Controls (n)	187	Stable CAD = 1499	Stable CAD = 1586	Stable CAD = 80
N(16)S(18)	Increased	Increased	NS	Increased
N(18)S(18)	Increased	NS	NS	NS
N(20)S(18)	Increased			
N(24)S(18)	Decreased	Decreased	Decreased	Decreased
N(24:1)S(18)		Increased	NS	Increased
N(16)S(18)/N(24)S(18)		Increased	Increased	Increased
N(18)S(18)/N(24)S(18)		Increased	Increased	Increased
N(24:1)S(18)/N(24)S(18)		Increased	Increased	Increased

(C) Major adverse cardiovascular event (by concentration)

Reference	[12]	[15]	[110]	[109]	[70]
Mortalities (n)	AMI 114	MACE 230	CHF 423	MACE 813	MACE 155
Other (n)	Unstable AP 92				
Other (n)	Stable AP 98				
Controls (n)	52		104	6892	419
N(16)S(18)		Increased		Increased	Positive (HR)
N(18)S(18)	NM		NM	Increased	
N(20)S(18)	NM		NM		NS
N(22)S(18)	NM	Increased	NM		
N(24)S(18)	NM	Increased	NM	Increased	NS
N(24:1)S(18)		Increased		Increased	NS
N(16)S(18)/N(24)S(18)		Increased		NS	NS
N(18)S(18)/N(24)S(18)				Increased	
N(20)S(18)/N(24)S(18)					NS
N(22)S(18)/N(24)S(18)		NS			
N(24:1)S(18)/N(24)S(18)		NS		Increased	NS
Total ceramides[a]	Increased for all		Increased		

(D) Acute coronary syndrome (by concentration)

Reference	[9]	[70]
ACS (n)	313	313
Stable CAD (n)	261	Stable AP = 261
N(16)S(18)	Increased in ACS	Increased in ACS
N(20)S(18)		Increased in ACS
N(24)S(18)	Increased in ACS	Increased in ACS
N(24:1)S(18)		Increased in ACS
N(16)S(18)/N(24)S(18)	Increased in ACS	Increased in ACS
N(20)S(18)/N(24)S(18)	NS	NS
N(24:1)S(18)/N(24)S(18)	NS	NS

(E) Type-2 diabetes

Reference	[78]	[77]	[73]	[74]	[74]	[58]	[75]	[75]	[75]	[75]	[76]	[76]	[76]	[77]	[73]	[58]
T2D (n)	14	14	15	1038		610	Assoc.	Assoc.	Assoc.	240	Assoc.	Assoc.	Assoc.	Correl.	Correl.	Correl.
Controls (n)	14	13	15 obese and 15 athletes	7007	3344	2145	1557			1000	2086					
Other info	Conc.	Conc.	Conc.	HR	HR	HR	Fasting glucose	Fasting insulin	HOMA-IR	T2D incidence	Fasting insulin	HOMA-IR	HOMA-B	Insulin sensitivity	Insulin sensitivity	Fasting glucose
N(16)S(18)	NS		NS	NS	NM	Positive	Positive	Positive	Positive	NS	Positive	Positive	NS		Inverse	NS
N(18)S(18)	Increased	Increased	Increased in T2D	Positive	Positive[b]	Positive	Positive	Positive	Positive	NS	Positive	Positive	Positive	Inverse	Inverse	Positive
N(18:1)S(18)		NS														
N(20)S(18)	Increased	Increased	Increased in T2D			Positive	NS	NS	NS	NS	Positive	Positive	Positive	Inverse	Inverse	NS
N(22)S(18)	Increased		NS			Positive					Positive	Positive	Positive		NM	Positive
N(22:1)S(18)							NS	NS	NS	NS						
N(22:9)S(18)							NS	NS	NS	NS						
N(22:10)S(18)							NS	NS	NS	NS						
N(24)S(18)	NS	NS	Increased in T2D	NM	NM	Positive[c]					NS[c]	Positive	NS	Inverse		NS
N(24:1)S(18)	NS	Increased	Increased in T2D	NM	NM									Inverse	Inverse	
N(24:2)S(18)	NS	Increased	Increased in T2D				NS	Positive	Positive	NS						
N(24:10)S(18)	NS	Increased	Increased in T2D				NS	NS	NS	NS						
N(26:9)S(18)							NS	NS	NS	NS						
N(28:9)S(18)							NS	NS	NS	NS						
N(30:9)S(18)							NS	NS	NS	NS						
N(30:10)S(18)							NS	Positive	Positive	NS						
N(32:11)S(18)							NS	Positive	Positive	NS						
N(16)S(18)/ N(24)S(18)						NM										NS
N(18)S(18)/ N(16)S(18)				Positive	Positive											
N(18)S(18)/ N(24)S(18)				Positive	Positive[b]	NM										NS
N(18)S(18)/ N(24:1)S(18)				Positive	NS[b]											
Total ceramides[a]	NS	Increased	NS											Inverse	NS	

Circulatory ceramide species that have been measured in cardiovascular disease settings in literature, alongside the total summation of species studied and further ratios of species reported in literature. Association is by hazard ratio or odds ratio, where significant includes a confidence interval (CI) of greater than 1. Positive: HR > 1.00 or a positive correlation coefficient, Negative/Inverse: significant HR < 1.00 or a negative correlation coefficient. Change by concentration is due to an alteration of the mean concentration from controls. MACE, major adverse cardiac events; NS, not significant; NM, not mentioned even though the species has been measured (likely means the result was NS). HR, hazard ratio; CHF, chronic heart failure; AP, angina pectoris; T2D, Type-2 Diabetes. [a]Sum ceramides; [b]depending on adjustment used; [c]composite of different species. Conc., by concentration; Assoc., association; Correl., correlation. "Increased in T2D" is in comparison to athletes. It should be noted "total ceramides" is the sum of the subset of ceramides that have been studied in a particular article, and not the full profile of ceramide species in circulation.

increased ratios potentially highlight an increased concentration of ceramide species with a shorter fatty acyl chain to those with larger carbon length. These ratios may highlight the involvement of *CERS* isoforms, such as *CERS1, CERS5*, *CERS6*, which have preference for shorter fatty acyls (C14–C18), while *CERS2, CERS3,* and *CERS4* utilise longer acyl chains (C18–C26) [71,72], however, more experiments are required to understand the mechanism of action and significance of these ratios, and their association with disease.

Overall, the significant correlations between the levels of most ceramide species studied to date demonstrate association with fatal outcomes in ACVD, the occurrence of MACE, and ACS. For the discovery of ceramides as predictive disease biomarkers, it is currently unknown whether the concentration of certain ceramides, ratios of ceramide species abundance, or measures of total concentration of ceramides, are more predictive of disease. As the current analyses of ceramide profiles show individual ceramide species acting in opposition, for example a negative association with disease was found for CER[N(24)S(18)] compared to the positive association with disease found for shorter ceramide species, the assessment of total summation of ceramides for disease prediction may provide deflated prediction results. Measurement and reporting of the full ceramide profile in large cohorts would aid our understanding of which species and ratios may be biomarkers of disease and health.

3.7. Type-2 diabetes

Ceramides have been strongly implicated in type-2 diabetes (T2D) as novel biomarkers of insulin resistance, but further targeted studies are required to expand the range of ceramide species studied. The associations reported in each of the current human studies for the individual ceramide species implicated in T2D risk are summarised in Table 1. This data highlights increased CER[N(18)S(18)] in T2D patients, positive hazard ratios with T2D incidence, positive associations with this species and markers of T2D such as fasting glucose, fasting insulin, HOMA-IR, and HOMA-B, as well as inverse correlations identified with this risk ceramide species and insulin sensitivity [58,73–78].

Other ceramides of note include CER[N(16)S(18)], which correlates with current diabetes risk markers [75,76]. However, this relationship of circulatory ceramides with both cardiovascular diseases and T2D is not clear, as some studies did not find significant associations or do not report associations for the measured lipids, suggesting lack of significance. Functional studies have begun to identify the role of ceramides in T2D. For example, inhibition of SPTLC via the drug myriocin ameliorates glucocorticoid-, saturated fat- and obesity-induced insulin resistance in rats [79].

3.8. Potential use of mendelian randomisation techniques

Observational epidemiology has led to a number of "blind alleys" where strongly associated putative atherosclerotic risk factors from observational epidemiological studies have, when modified in clinical trials, proven not to affect disease risk; examples include plasma HDL-cholesterol [80] and vitamins. The massive resource costs of drug development and clinical trials aiming to modify putative risk factors, which turn out to be non-causal, could perhaps be avoided in the future through the use of Mendelian randomisation (MR), a genetic approach to determining causality on which there is now extensive literature [81–87]. The concept underlying MR is outlined in Fig. 2, with specific reference to ceramides. MR can be used to investigate the causality of putative ACVD biomarkers; broadly speaking, if DNA variants can be discovered with effects on ACVD risk, which congruently influence the levels of associated biomarkers, causality can be inferred for the biomarkers on ACVD [88]. For example, MR was the key technique in establishing the causality of plasma levels of lipoprotein(a) in ACVD [89].

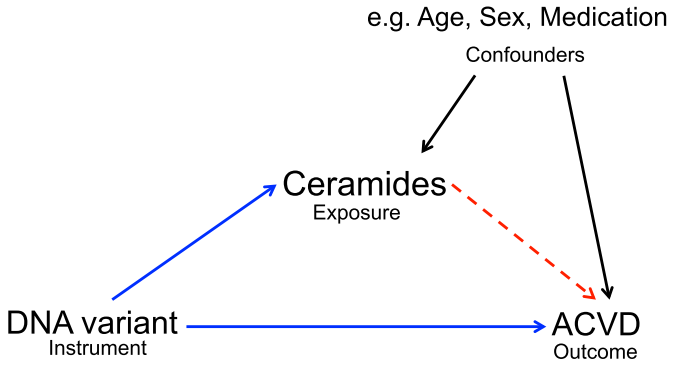

Fig. 2. Mendelian randomisation.
This figure depicts the principles of Mendelian randomisation. If a DNA variant (SNP) associates with a trait (ceramide species) and disease (CAD) independently, Mendelian randomisation can be used to confirm the causality of the trait with the disease, as DNA variants are not affected by confounding factors. For example, if a DNA variant affects the levels of a ceramide species in circulation, then the differences in that ceramide species will be lifelong differences, as genotype is allocated at conception. Both this predetermined effect of the DNA variant on ceramide species levels, and a GWAS association of the same variant with risk of ACVD, would give strong support for a causal association with ceramides and ACVD risk.

Although there is a growing body of evidence that blood ceramide concentrations are associated with CAD risk and other cardiovascular diseases such as T2D, more work is needed to provide definitive answers and confirm these associations. The identification of highly heritable ceramide species and the genetic variants responsible enables MR to be applied to this class of bioactive lipid mediators implicated in ACVD risk, to confirm or refute some hypothesised associations for specific ceramide species. While there are drugs available that target the major metabolic enzymes in the ceramide biosynthetic pathway, there are no selective drugs that can alter the levels of specific ceramides, to date. Thus, studies analysing larger numbers of circulating ceramides, with increased study sample sizes and including different populations, as well as molecular experimentation, are needed to further our understanding of the mechanisms behind the role of ceramides in these diseases.

4. Genetic insights

4.1. Current genetic studies of ceramides

Genome-wide association studies (GWAS) have identified common DNA variants influencing circulating ceramide levels. In 2009, a discovery GWAS was undertaken to identify genes influencing sphingolipid production and metabolism [90]. This involved the genetic analyses of seven ceramide species, namely: CER[N(16)S(18)], CER[N(18)S(18)], CER[N(20)S(18)], CER[N(22)S(18)], CER[N(23)S(18)], CER[N(24:1)S(18)], CER[N(24)S(18)], and summed total ceramides, which were profiled in 4400 participants from plasma or serum of five European populations [91,92]. Polymorphisms at *CERS4* were associated with the ceramide species CER[N(20)S(18)] ($p < 5 \times 10^{-8}$) in the South Tyrol and Croatian populations.

The studies also identified a polymorphism in *SPTLC3* that associated with five plasma ceramides (CER[N(16)S(18)], CER[N(22)S(18)], CER[N(23)S(18)], CER[N(24)S(18)], CER[N(24:1)S(18)]). Of the variants identified, those in *SPTLC3* associated with myocardial infarction incidence in the study of 4110 participants from five European populations and a replication study in 4034 participants from the same populations [90,91]. The GWAS association of circulating ceramide species with variants in *SPTLC3* has now been repeated in a number of studies [90–92], which have been identified as confirmed liver expression quantitative trait loci (eQTLs) of *SPTLC3* [93,94]. However, variants in *SPTLC3* have not associated with myocardial infarction in large genetic analyses of ACVD, e.g. 60,000 myocardial infarction patients compared to controls [95]. The locus does not show significant disease associations through PheWAS analysis in UK Biobank, and to date, MR has not confirmed a causal relationship between ceramides with ACVD through DNA variants in *SPTLC3* [93].

Recent GWAS have also identified common variants in other genes of ceramide biosynthetic enzymes: sphingosine 1-phosphate phosphatase 1 (*SGPP1*) and dihydroceramide desaturase (*DEGS1)* [93]. A rare non-synonymous variant in *DEGS1* has also been identified to increase concentrations of dihydroceramides [96].

While MR has not confirmed a causal role for ceramides in ACVD risk, ceramides are substantially heritable; variation in ceramides is influenced by genetic factors. Six ceramides (CER[N(16)S(18)], CER[N(18)S(18)], CER[N(20)S(18)], CER[N(22)S(18)], CER[N(24)S(18)], CER[N(24:1)S(18)]) were analysed in a study of a broad number of lipids in 1212 participants from 42 Mexican American families [97]. A median estimate of heritability, the variation in ceramide levels to due genetic factors, was reported at 45% for all ceramides, using family-based variance-components analyses. Other estimates of narrow-sense heritability have estimated the heritability of circulating ceramides to be between 9% and 62% [93,97–99].

4.2. Ceramide metabolising enzymes implicated in GWAS for cardiovascular traits

GWAS for cardiovascular traits have identified associations between common variation in the genes involved in ceramide biosynthesis and certain cardiovascular disease-related traits (Table 2). Of note, DNA variants have been identified near genes of the ceramide pathway that associate with LDL-cholesterol and HDL-cholesterol [90,100–102]. Perhaps particularly noteworthy are the association of variants near *ASAH1* with atrial fibrillation and that of *CERS2* variants with glycated haemoglobin A1c. *ASAH1* is the gene for ceramidases, the enzymes that degrade ceramides to sphingosine (as before: biochemistry section and Fig. 1A). The variant rs7508 near *ASAH1* was identified in three GWAS studies of atrial fibrillation with association *p*-values of 6×10^{-10} - 2×10^{-21} and odds ratios of 1.07–1.10. These studies were a meta-analyses of common and rare variant association studies of 40,277 individuals with atrial fibrillation and 247,228 controls [103], a GWAS study of 60,620 cases and 970,216 controls [104], and a multi-ethnic meta-analysis of more than half a million participants including 65,446 cases [105]. The variant is found in the 3′untranslated region of the gene and genotype is associated with RNA expression of *ASAH1* in multiple tissues including the heart left ventricle and atrial appendage, where the risk allele has increased expression of *ASAH1* in the heart tissues [94]. This potentially implicates an alteration in tissue or circulating ceramide levels in the pathogenesis of atrial fibrillation. However, an analysis of total ceramides in atrial biopsies from 54 patients with atrial fibrillation or sinus rhythm did not identify a difference in total ceramide levels between the two groups [106]. Circulating ceramide species in patients with atrial fibrillation have not thus far been investigated. Encouragingly, in 2020 a GWAS of T2D in 433,540 East Asian individuals identified a GWAS significant association with variant and confirmed eQTL of *ASAH1* (rs34642578) [107] (Table 1).

A missense variant (rs267738) in the *CERS2* gene has been identified at GWAS to associate with HDL cholesterol, cathepsin S measurements, glomerular filtration rate, serum creatinine measurement and haemoglobin A1C measurement ($p = 1 \times 10^{-9}$ - 9×10^{-17}). The variant is an eQTL of many genes, including *CERS2* where the risk allele has decreased expression of *CERS2* in the testis and tibial artery [94].

Genes encoding the enzymes of the *de novo* ceramide biosynthesis have been studied for prospective association with hypertension (n = 2523) [108]. The study undertook a network analysis on 162 SNPs in 84 genes of sphingolipid metabolism. The variance explained by the ceramide biosynthesis network was more than 50% in a subpopulation of hypertensive participants.

To fully address causality of ceramides in ACVD, large cohort analyses with genetic data available are needed to profile each circulating ceramide species. This may identify specific ceramide species with genetic associations that would allow the issue of causality to be fully addressed.

5. Conclusions and future directions

Cardiovascular diseases remain the most prevalent cause of death globally despite highly impactful interventions on proven risk factors. New biomarkers remain needed to more precisely stratify individuals at high risk of disease and events. Lipids have key roles in cardiovascular disease, but even as mass spectrometry techniques and lipidomics applications have expanded, there are as yet few studies with substantial sample sizes measuring the large number of lipid species now identifiable. Bioactive lipid mediators of inflammation found in circulation may reflect an underlying predisposition to cardiovascular disease. Ceramide species from the sphingolipid class of lipids may be causing chronic underlying apoptosis, mediating inflammation and priming the vasculature for atherosclerosis or diabetes, adding to other cardiovascular risk factors. Here, their implications as potential risk biomarkers of ACVD are described. We conclude that larger cohort studies, together with functional studies, are needed to fully decipher this relationship. Their causality in ACVD risk is currently not clear, and large-scale genetic studies (for example, in the UK Biobank population) incorporating full coverage of the many species of ceramides currently measurable would be a powerful means of addressing this question. Identification of the most genetically influenced lipids may be the first step to identify the most promising novel lipid species for focused studies in large cohorts. Continued identification of genome-associated variants of circulatory ceramide concentrations will allow for further Mendelian randomisation analyses with ACVD, to allow for targeting specific ceramide species for use in ACVD diagnosis, risk stratification, and treatment.

Table 2
Genes of key ceramide metabolising enzymes (proteins) identify near DNA variants associated with cardiovascular traits at GWAS. Data was assessed via GWAS catalog (up to April 2021).

Enzyme [Protein]	Gene	GWAS association
Ceramide synthase	*CERS2*	HDL cholesterol [102]
		Glycated haemoglobin A1C [112]
		Glomerular filtration rate [113,114]
		Serum creatinine [113]
		Apolipoprotein A1 levels [115]
	CERS3	Childhood BMI [116]
	CERS5	Hypertension and blood pressure [117–119]
	CERS6	Triglyceride levels [115]
Ceramide transfer protein	*CERT1*	LDL cholesterol [120]
Neutral ceramidase	*ASAH1*	Atrial fibrillation [103–105]
		Type-2 diabetes [107]

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CRediT authorship contribution statement

Kathryn A. McGurk: Conceptualization, Writing – original draft. **Bernard D. Keavney:** Writing – review & editing. **Anna Nicolaou:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] I.E. Hoefer, S. Steffens, M. Ala-Korpela, M. Bäck, L. Badimon, M.L. Bochaton-Piallat, C.M. Boulanger, G. Caligiuri, S. Dimmeler, J. Egido, P.C. Evans, T. Guzik, B.R. Kwak, U. Landmesser, M. Mayr, C. Monaco, G. Pasterkamp, J. Tuñón, C. Weber, Novel methodologies for biomarker discovery in atherosclerosis, Eur. Heart J. 36 (2015) 2635–2642.

[2] V.D.F. De Mello, M. Lankinen, U. Schwab, M. Kolehmainen, S. Lehto, T. Seppänen-Laakso, M. Orešič, L. Pulkkinen, M. Uusitupa, A.T. Erkkilä, Link between plasma ceramides, inflammation and insulin resistance: association with serum IL-6 concentration in patients with coronary heart disease, Diabetologia 52 (2009) 2612–2615, https://doi.org/10.1007/s00125-009-1482-9.

[3] I. Majumdar, L.D. Mastrandrea, Serum sphingolipids and inflammatory mediators in adolescents at risk for metabolic syndrome, Endocrine 41 (2012) 442–449, https://doi.org/10.1007/s12020-011-9589-4.

[4] W.L. Holland, A.C. Adams, J.T. Brozinick, H.H. Bui, Y. Miyauchi, C.M. Kusminski, S.M. Bauer, M. Wade, E. Singhal, C.C. Cheng, K. Volk, M.S. Kuo, R. Gordillo, A. Kharitonenkov, P.E. Scherer, An FGF21-adiponectin-ceramide axis controls energy expenditure and insulin action in mice, Cell Metabol. 17 (2013) 790–797, https://doi.org/10.1016/j.cmet.2013.03.019.

[5] C. Tao, A. Sifuentes, W.L. Holland, Regulation of glucose and lipid homeostasis by adiponectin: effects on hepatocytes, pancreatic β cells and adipocytes, Best Pract, Res. Clin. Endocrinol. Metab. 28 (2014) 43–58, https://doi.org/10.1016/j.beem.2013.11.0035.

[6] B. Vandanmagsar, Y.H. Youm, A. Ravussin, J.E. Galgani, K. Stadler, R.L. Mynatt, E. Ravussin, J.M. Stephens, V.D. Dixit, The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance, Nat. Med. 17 (2011) 179–189, https://doi.org/10.1038/nm.2279.

[7] L.M. Obeid, C.M. Linardic, L.A. Karolak, Y.A. Hannun, Programmed cell death induced by ceramide, Science 259 (1993) 1769–1771, https://doi.org/10.1126/science.8456305, 80-.

[8] S. Chatterjee, Sphingolipids in atherosclerosis and vascular biology, Arterioscler. Thromb. Vasc. Biol. 18 (1998) 1523–1533, https://doi.org/10.1161/01.ATV.18.10.1523.

[9] J.M. Cheng, M. Suoniemi, I. Kardys, T. Vihervaara, S.P.M. de Boer, K. M. Akkerhuis, M. Sysi-Aho, K. Ekroos, H.M. Garcia-Garcia, R.M. Oemrawsingh, E. Regar, W. Koenig, P.W. Serruys, R.J. van Geuns, E. Boersma, R. Laaksonen, Plasma concentrations of molecular lipid species in relation to coronary plaque characteristics and cardiovascular outcome: Results of the ATHEROREMO-IVUS study, Atherosclerosis 243 (2015) 560–566, https://doi.org/10.1016/j.atherosclerosis.2015.10.022.

[10] M. Chatterjee, D. Rath, J. Schlotterbeck, J. Rheinlaender, B. Walker-Allgaier, N. Alnaggar, M. Zdanyte, I. Müller, O. Borst, T. Geisler, T.E. Schäffer, M. Lämmerhofer, M. Gawaz, Regulation of oxidized platelet lipidome: implications for coronary artery disease, Eur. Heart J. 38 (2017) 1993–2005, https://doi.org/10.1093/eurheartj/ehx146.

[11] K. Tarasov, K. Ekroos, M. Suoniemi, D. Kauhanen, T. Sylvänne, R. Hurme, I. Gouni-Berthold, H.K. Berthold, M.E. Kleber, R. Laaksonen, W. März, Molecular lipids identify cardiovascular risk and are efficiently lowered by simvastatin and PCSK9 deficiency, J. Clin. Endocrinol. Metab. 99 (2014) 45–52, https://doi.org/10.1210/jc.2013-2559.

[12] W. Pan, J. Yu, R. Shi, L. Yan, T. Yang, Y. Li, Z. Zhang, G. Yu, Y. Bai, E. H. Schuchman, X. He, G. Zhang, Elevation of ceramide and activation of secretory acid sphingomyelinase in patients with acute coronary syndromes, Coron. Artery Dis. 25 (2014) 230–235, https://doi.org/10.1097/MCA.0000000000000079.

[13] R. Laaksonen, K. Ekroos, M. Sysi-Aho, M. Hilvo, T. Vihervaara, D. Kauhanen, M. Suoniemi, R. Hurme, W. März, H. Scharnagl, T. Stojakovic, E. Vlachopoulou, M.L. Lokki, M.S. Nieminen, R. Klingenberg, C.M. Matter, T. Hornemann, P. Jüni, N. Rodondi, L. Räber, S. Windecker, B. Gencer, E.R. Pedersen, G.S. Tell, O. Nygård, F. Mach, J. Sinisalo, T.F. Lüscher, Plasma ceramides predict cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes beyond LDL-cholesterol, Eur. Heart J. 37 (2016) 1967–1976, https://doi.org/10.1093/eurheartj/ehw148.

[14] D. Kauhanen, M. Sysi-Aho, K.M. Koistinen, R. Laaksonen, J. Sinisalo, K. Ekroos, Development and validation of a high-throughput LC–MS/MS assay for routine measurement of molecular ceramides, Anal. Bioanal. Chem. 408 (2016) 3475–3483, https://doi.org/10.1007/s00216-016-9425-z.

[15] D.D. Wang, E. Toledo, A. Hruby, B.A. Rosner, W.C. Willett, Q. Sun, C. Razquin, Y. Zheng, M. Ruiz-Canela, M. Guasch-Ferré, D. Corella, E. Gómez-Gracia, M. Fiol, R. Estruch, E. Ros, J. Lapetra, M. Fito, F. Aros, L. Serra-Majem, C.H. Lee, C. B. Clish, L. Liang, J. Salas-Salvadó, M.A. Martínez-González, F.B. Hu, Plasma ceramides, mediterranean diet, and incident cardiovascular disease in the PREDIMED trial, Circulation 135 (2017) 2028–2040, https://doi.org/10.1161/CIRCULATIONAHA.116.024261.

[16] Y.A. Hannun, L.M. Obeid, Principles of bioactive lipid signalling: lessons from sphingolipids, Nat. Rev. Mol. Cell Biol. 9 (2008) 139–150, https://doi.org/10.1038/nrm2329.

[17] W.L. Holland, S.A. Summers, Sphingolipids, insulin resistance, and metabolic disease: new insights from in vivo manipulation of sphingolipid metabolism, Endocr. Rev. 29 (2008) 381–402, https://doi.org/10.1210/er.2007-0025.

[18] Y. a Hannun, Functions of ceramide in coordinating cellular responses to stress, Science 274 (1996) 1855–1859, https://doi.org/10.1126/science.274.5294.1855.

[19] D.K. Perry, Y.A. Hannun, The role of ceramide in cell signaling, Biochim. Biophys. Acta 1436 (1998) 233–243.

[20] Y. Masukawa, H. Narita, H. Sato, A. Naoe, N. Kondo, Y. Sugai, T. Oba, R. Homma, J. Ishikawa, Y. Takagi, T. Kitahara, Comprehensive quantification of ceramide species in human stratum corneum, J. Lipid Res. 50 (2009) 1708–1719, https://doi.org/10.1194/jlr.D800055-JLR200.

[21] Y. Masukawa, H. Narita, E. Shimizu, N. Kondo, Y. Sugai, T. Oba, R. Homma, J. Ishikawa, Y. Takagi, T. Kitahara, Y. Takema, K. Kita, Characterization of overall ceramide species in human *stratum corneum*, J. Lipid Res. 49 (2008) 1466–1476, https://doi.org/10.1194/jlr.M800014-JLR200.

[22] N. Bartke, Y.A. Hannun, Bioactive sphingolipids: metabolism and function, J. Lipid Res. 50 (2009) S91–S96, https://doi.org/10.1194/jlr.R800080-JLR200.

[23] B.T. Bikman, S.A. Summers, Ceramides as modulators of cellular and whole-body metabolism, J. Clin. Invest. 121 (2011) 4222–4230, https://doi.org/10.1172/JCI57144.

[24] W. Khovidhunkit, M.-S. Kim, R. a Memon, J.K. Shigenaga, A.H. Moser, K. R. Feingold, C. Grunfeld, Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host, J. Lipid Res. 45 (2004) 1169–1196, https://doi.org/10.1194/jlr.R300019-JLR200.

[25] R. Bose, M. Verheij, A. Haimovitz-Friedman, K. Scotto, Z. Fuks, R. Kolesnick, Ceramide synthase mediates daunorubicin-induced apoptosis: an alternative mechanism for generating death signals, Cell 82 (1995) 405–414, https://doi.org/10.1016/0092-8674(95)90429-8.

[26] K. Wiegmann, S. Schütze, T. Machleidt, D. Witte, M. Krönke, Functional dichotomy of neutral and acidic sphingomyelinases in tumor necrosis factor signaling, Cell 78 (1994) 1005–1015, https://doi.org/10.1016/0092-8674(94)90275-5.

[27] S. Marathe, S.L. Schissel, M.J. Yellin, N. Beatini, R. Mintzer, K.J. Williams, I. Tabas, Human vascular endothelial cells are a rich and regulatable source of secretory sphingomyelinase, J. Biol. Chem. 273 (1998) 4081–4088.

[28] M. Uhlen, L. Fagerberg, B.M. Hallstrom, C. Lindskog, P. Oksvold, A. Mardinoglu, A. Sivertsson, C. Kampf, E. Sjostedt, A. Asplund, I. Olsson, K. Edlund, E. Lundberg, S. Navani, C.A.-K. Szigyarto, J. Odeberg, D. Djureinovic, J.O. Takanen, S. Hober, T. Alm, P.-H. Edqvist, H. Berling, H. Tegel, J. Mulder, J. Rockberg, P. Nilsson, J. M. Schwenk, M. Hamsten, K. von Feilitzen, M. Forsberg, L. Persson, F. Johansson, M. Zwahlen, G. von Heijne, J. Nielsen, F. Ponten, Tissue-based map of the human proteome, 80-, Science 347 (2015), https://doi.org/10.1126/science.1260419, 1260419–1260419.

[29] A.C. Kendall, A. Nicolaou, Bioactive lipid mediators in skin inflammation and immunity, Prog. Lipid Res. 52 (2013) 141–164, https://doi.org/10.1016/j.plipres.2012.10.003.

[30] P. Libby, P. Theroux, Pathophysiology of coronary artery disease, Circulation 111 (2005) 3481–3488, https://doi.org/10.1161/CIRCULATIONAHA.105.537878.

[31] S.A.F. Morad, M.C. Cabot, Ceramide-orchestrated signalling in cancer cells, Nat. Rev. Canc. 13 (2013) 51–65, https://doi.org/10.1038/nrc3398.

[32] L.J. Siskind, S. Fluss, M. Bui, M. Colombini, Sphingosine forms channels in membranes that differ greatly from those formed by ceramide, J. Bioenerg. Biomembr. 37 (2005) 227–236, https://doi.org/10.1007/s10863-005-6632-2.

[33] J. Stiban, L. Caputo, M. Colombini, Ceramide synthesis in the endoplasmic reticulum can permeabilize mitochondria to proapoptotic proteins, J. Lipid Res. 49 (2008) 625–634, https://doi.org/10.1194/jlr.M700480-JLR200.

[34] W. Zheng, J. Kollmeyer, H. Symolon, A. Momin, E. Munter, E. Wang, S. Kelly, J. C. Allegood, Y. Liu, Q. Peng, H. Ramaraju, M.C. Sullards, M. Cabot, A.H. Merrill, Ceramides and other bioactive sphingolipid backbones in health and disease: lipidomic analysis, metabolism and roles in membrane structure, dynamics, signaling and autophagy, Biochim. Biophys. Acta Biomembr. 1758 (2006) 1864–1884, https://doi.org/10.1016/j.bbamem.2006.08.009.

[35] P. Libby, P.M. Ridker, G.K. Hansson, Progress and challenges in translating the biology of atherosclerosis, Nature 473 (2011) 317–325, https://doi.org/10.1038/nature10146.

[36] Z. Mallat, a Tedgui, Apoptosis in the vasculature: mechanisms and functional importance, Br. J. Pharmacol. 130 (2000) 947–962, https://doi.org/10.1038/sj.bjp.0703407.

[37] Y. Lee, Å.B. Gustafsson, Role of apoptosis in cardiovascular disease, Apoptosis 14 (2009) 536–548, https://doi.org/10.1007/s10495-008-0302-x.

[38] A.E. Bielawska, J.P. Shapiro, L. Jiang, H.S. Melkonyan, C. Piot, C.L. Wolfe, L. D. Tomei, Y.A. Hannun, S.R. Umansky, Ceramide is involved in triggering of cardiomyocyte apoptosis induced by ischemia and reperfusion, Am. J. Pathol. 151 (1997) 1257–1263.

[39] N. Sattar, D.W. McCarey, H. Capell, I.B. McInnes, Explaining how “high-grade” systemic inflammation accelerates vascular risk in rheumatoid arthritis, Circulation 108 (2003) 2957–2963, https://doi.org/10.1161/01.CIR.0000099844.31524.05.

[40] N.Y. Villa, B.R. Kupchak, I. Garitaonandia, J.L. Smith, E. Alonso, C. Alford, L.A. Cowart, Y.A. Hannun, T.J. Lyons, Sphingolipids Function as Downstream Effectors of a Fungal, (2009) 866–875. doi:10.1124/mol.108.049809.

[41] M. Lankinen, U. Schwab, M. Kolehmainen, J. Paananen, H. Nygren, T. Seppanen-Laakso, K. Poutanen, T. Hyotylainen, U. Riserus, M.J. Savolainen, J. Hukkanen, L. Brader, M. Marklund, F. Rosqvist, K. Hermansen, L. Cloetens, G. Onning, I. Thorsdottir, I. Gunnarsdottir, B. Akesson, L.O. Dragsted, M. Uusitupa, M. Oresic, A healthy nordic diet alters the plasma lipidomic profile in adults with features of metabolic syndrome in a multicenter randomized dietary intervention, J. Nutr. 146 (2016) 662–672, https://doi.org/10.3945/jn.115.220459.

[42] C.L. Kien, J.Y. Bunn, M.E. Poynter, R. Stevens, J. Bain, O. Ikayeva, N. K. Fukagawa, C.M. Champagne, K.I. Crain, T.R. Koves, D.M. Muoio, A lipidomics analysis of the relationship between dietary fatty acid composition and insulin sensitivity in young adults, Diabetes 62 (2013) 1054–1063, https://doi.org/10.2337/db12-0363.

[43] J. Myers, Exercise and cardiovascular health, Circulation 107 (2003) 1–4, https://doi.org/10.1161/01.CIR.0000048890.59383.8D.

[44] J.J. Dubé, F. Amati, F.G.S. Toledo, M. Stefanovic-Racic, A. Rossi, P. Coen, B. H. Goodpaster, Effects of weight loss and exercise on insulin resistance, and intramyocellular triacylglycerol, diacylglycerol and ceramide, Diabetologia 54 (2011) 1147–1156, https://doi.org/10.1007/s00125-011-2065-0.

[45] S.M. Turpin, H.T. Nicholls, D.M. Willmes, A. Mourier, S. Brodesser, C. M. Wunderlich, J. Mauer, E. Xu, P. Hammerschmidt, H.S. Brönneke, A. Trifunovic, G. Losasso, F.T. Wunderlich, J.W. Kornfeld, M. Blüher, M. Krönke,

J.C. Brüning, Obesity-induced CerS6-dependent C16:0 ceramide production promotes weight gain and glucose intolerance, Cell Metabol. 20 (2014) 678–686, https://doi.org/10.1016/j.cmet.2014.08.002.
[46] D. Gosejacob, P.S. Jäger, K. Vom Dorp, M. Frejno, A.C. Carstensen, M. Köhnke, J. Degen, P. Dörmann, M. Hoch, Ceramide synthase 5 is essential to maintain C16:0-Ceramide pools and contributes to the development of diet-induced obesity, J. Biol. Chem. 291 (2016) 6989–7003, https://doi.org/10.1074/jbc.M115.691212.
[47] S. Raichur, B. Brunner, M. Bielohuby, G. Hansen, A. Pfenninger, B. Wang, J. C. Bruning, P.J. Larsen, N. Tennagels, The role of C16:0 ceramide in the development of obesity and type 2 diabetes: CerS6 inhibition as a novel therapeutic approach, Mol. Metab. 21 (2019) 36–50, https://doi.org/10.1016/j.molmet.2018.12.008.
[48] L.F. León-Aguilar, M. Croyal, V. Ferchaud-Roucher, F. Huang, L.A. Marchat, A. Barraza-Villarreal, I. Romieu, U. Ramakrishnan, M. Krempf, K. Ouguerram, R. Mercado-Camargo, F. Bolaños-Jiménez, Maternal obesity leads to long-term altered levels of plasma ceramides in the offspring as revealed by a longitudinal lipidomic study in children, Int. J. Obes. 43 (2019) 1231–1243, https://doi.org/10.1038/s41366-018-0291-y.
[49] P. Wiesner, K. Leidl, A. Boettcher, G. Schmitz, G. Liebisch, Lipid profiling of FPLC-separated lipoprotein fractions by electrospray ionization tandem mass spectrometry, J. Lipid Res. 50 (2009) 574–585, https://doi.org/10.1194/jlr.D800028-JLR200.
[50] C.M. Devlin, A.R. Leventhal, G. Kuriakose, E.H. Schuchman, K.J. Williams, I. Tabas, Acid sphingomyelinase promotes lipoprotein retention within early atheromata and accelerates lesion progression, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 1723–1730, https://doi.org/10.1161/ATVBAHA.108.173344.
[51] W. Li, X. Yang, S. Xing, F. Bian, W. Yao, X. Bai, T. Zheng, G. Wu, S. Jin, Endogenous ceramide contributes to the transcytosis of oxldl across endothelial cells and promotes its subendothelial retention in vascular wall, Oxid. Med. Cell. Longev. 2014 (2014) 823071, https://doi.org/10.1155/2014/823071.
[52] Y.-M. Wei, X. Li, J. Xiong, J.M. Abais, M. Xia, K.M. Boini, Y. Zhang, P.-L. Li, Attenuation by statins of membrane raft-redox signaling in coronary arterial endothelium, J. Pharmacol. Exp. Therapeut. 345 (2013) 170–179, https://doi.org/10.1124/jpet.112.201442.
[53] I. Ichi, K. Nakahara, Y. Miyashita, A. Hidaka, S. Kutsukake, K. Inoue, T. Maruyama, Y. Miwa, M. Harada-Shiba, M. Tsushima, S. Kojo, Association of ceramides in human plasma with risk factors of atherosclerosis, Lipids 41 (2006) 859–863, https://doi.org/10.1007/s11745-006-5041-6.
[54] T.W.K. Ng, E.M.M. Ooi, G.F. Watts, D.C. Chan, P.J. Meikle, P.H.R. Barrett, Association of plasma ceramides and sphingomyelin with VLDL apoB-100 fractional catabolic rate before and after rosuvastatin treatment, J. Clin. Endocrinol. Metab. 100 (2015) 2497–2501, https://doi.org/10.1210/jc.2014-4348.
[55] Y.A. Hannun, L.M. Obeid, Many ceramides, J. Biol. Chem. 286 (2011) 27855–27862, https://doi.org/10.1074/jbc.R111.254359.
[56] M.M. Mielke, V.V.R. Bandaru, D. Han, Y. An, S.M. Resnick, L. Ferrucci, N. J. Haughey, Demographic and clinical variables affecting mid- to late-life trajectories of plasma ceramide and dihydroceramide species, Aging Cell 14 (2015) 1014–1023, https://doi.org/10.1111/acel.12369.
[57] V. Vozella, A. Basit, F. Piras, N. Realini, A. Armirotti, P. Bossù, F. Assogna, S. L. Sensi, G. Spalletta, D. Piomelli, Elevated plasma ceramide levels in post-menopausal women: a cross-sectional study, Aging (Albany. NY) 11 (2019) 73–88, https://doi.org/10.18632/aging.101719.
[58] P.N. Jensen, A.M. Fretts, C. Yu, A.N. Hoofnagle, J.G. Umans, B.V. Howard, C. M. Sitlani, D.S. Siscovick, I.B. King, N. Sotoodehnia, B. McKnight, R.N. Lemaitre, Circulating sphingolipids, fasting glucose, and impaired fasting glucose: the Strong Heart Family Study, EBioMedicine 41 (2019) 44–49, https://doi.org/10.1016/j.ebiom.2018.12.046.
[59] S.A. Lightle, J.I. Oakley, M.N. Nikolova-Karakashian, Activation of sphingolipid turnover and chronic generation of ceramide and sphingosine in liver during aging, Mech. Ageing Dev. 120 (2000) 111–125, https://doi.org/10.1016/S0047-6374(00)00191-3.
[60] K. Kobayashi, E. Nagata, K. Sasaki, M. Harada-Shiba, S. Kojo, H. Kikuzaki, Increase in secretory sphingomyelinase activity and specific ceramides in the aorta of apolipoprotein E knockout mice during aging, Biol. Pharm. Bull. 36 (2013) 1192–1196, https://doi.org/10.1248/bpb.b13-00180.
[61] J. Ohanian, A. Liao, S.P. Forman, V. Ohanian, Age-related remodeling of small arteries is accompanied by increased sphingomyelinase activity and accumulation of long-chain ceramides, Phys. Rep. 2 (2014) 1–12, https://doi.org/10.14814/phy2.12015.
[62] R.P. Rao, C. Yuan, J.C. Allegood, S.S. Rawat, M.B. Edwards, X. Wang, A. H. Merrill, U. Acharya, J.K. Acharya, Ceramide transfer protein function is essential for normal oxidative stress response and lifespan, Proc. Natl. Acad. Sci. U.S.A. 104 (2007) 11364–11369, https://doi.org/10.1073/pnas.0705049104.
[63] L.G. Wooten-Blanks, P. Song, C.E. Senkal, B. Ogretmen, Mechanisms of ceramide-mediated repression of the human telomerase reverse transcriptase promoter via deacetylation of Sp3 by histone deacetylase 1, Faseb. J. 21 (2007) 3386–3397, https://doi.org/10.1096/fj.07-8621com.
[64] A.R. Smith, F. Visioli, B. Frei, T.M. Hagen, Age-related changes in endothelial nitric oxide synthase phosphorylation and nitric oxide dependent vasodilation: evidence for a novel mechanism involving sphingomyelinase and ceramide-activated phosphatase 2A, Aging Cell 5 (2006) 391–400, https://doi.org/10.1111/j.1474-9726.2006.00232.x.
[65] H. Kulkarni, P.J. Meikle, M. Mamtani, J.M. Weir, C.K. Barlow, J.B. Jowett, C. Bellis, T.D. Dyer, M.P. Johnson, D.L. Rainwater, L. Almasy, M.C. Mahaney, A. G. Comuzzie, J. Blangero, J.E. Curran, Plasma lipidomic profile signature of hypertension in mexican american families: specific role of diacylglycerols, Hypertension 62 (2013) 621–626, https://doi.org/10.1161/HYPERTENSIONAHA.113.01396.
[66] L.J.A. Spijkers, R.F.P. van den Akker, B.J.A. Janssen, J.J. Debets, J.G.R. de Mey, E.S.G. Stroes, B.J.H. van den Born, D.S. Wijesinghe, C.E. Chalfant, L. MacAleese, G.B. Eijkel, R.M.A. Heeren, A.E. Alewijnse, S.L.M. Peters, Hypertension is associated with marked alterations in sphingolipid biology: a potential role for ceramide, PloS One 6 (2011) 1–9, https://doi.org/10.1371/journal.pone.0021817.
[67] L. Chun, Z. Junlin, W. Aimin, L. Niansheng, C. Benmei, L. Minxiang, Inhibition of ceramide synthesis reverses endothelial dysfunction and atherosclerosis in streptozotocin-induced diabetic rats, Diabetes Res. Clin. Pract. 93 (2011) 77–85, https://doi.org/10.1016/j.diabres.2011.03.017.
[68] J. Moral-Sanz, T. Gonzalez, C. Menendez, M. David, L. Moreno, A. Macias, J. Cortijo, C. Valenzuela, F. Perez-Vizcaino, A. Cogolludo, Ceramide inhibits Kv currents and contributes to TP-receptor-induced vasoconstriction in rat and human pulmonary arteries, Am. J. Physiol. Cell Physiol. 301 (2011) C186–C194, https://doi.org/10.1152/ajpcell.00243.2010.
[69] P.L. Li, D.X. Zhang, A.P. Zou, W.B. Campbell, Effect of ceramide on K(Ca) channel activity and vascular tone in coronary arteries, Hypertension 33 (1999) 1441–1446, https://doi.org/10.1161/01.HYP.33.6.1441.
[70] S. Anroedh, M. Hilvo, K.M. Akkerhuis, D. Kauhanen, K. Koistinen, R. Oemrawsingh, P. Serruys, R.-J. van Geuns, E. Boersma, R. Laaksonen, I. Kardys, Plasma concentrations of molecular lipid species predict long-term clinical outcome in coronary artery disease patients, J. Lipid Res. 59 (2018) 1729–1737, https://doi.org/10.1194/jlr.p081281.
[71] Y. Mizutani, A. Kihara, Y. Igarashi, Mammalian Lass 6 and its related family members regulate synthesis of specific ceramides, Biochem. J. 390 (2005) 263–271, https://doi.org/10.1042/BJ20050291.
[72] R. Tidhar, I.D. Zelnik, G. Volpert, S. Ben-Dor, S. Kelly, A.H. Merrill, A. H. Futerman, Eleven residues determine the acyl chain specificity of ceramide synthases, J. Biol. Chem. 287 (2018) 3197–3206, https://doi.org/10.1074/jbc.RA118.001936.
[73] B.C. Bergman, J.T. Brozinick, A. Strauss, S. Bacon, A. Kerege, H.H. Bui, P. Sanders, P. Siddall, M.S. Kuo, L. Perreault, Serum sphingolipids: relationships to insulin sensitivity and changes with exercise in humans, Am. J. Physiol. Endocrinol. Metab. 309 (2015) 398–408, https://doi.org/10.1152/ajpendo.00134.2015.
[74] M. Hilvo, T. Salonurmi, A.S. Havulinna, D. Kauhanen, E.R. Pedersen, G.S. Tell, K. Meyer, A.M. Teeriniemi, T. Laatikainen, P. Jousilahti, M.J. Savolainen, O. Nygård, V. Salomaa, R. Laaksonen, Ceramide stearic to palmitic acid ratio predicts incident diabetes, Diabetologia 61 (2018) 1424–1434, https://doi.org/10.1007/s00125-018-4590-6.
[75] I.J. Neeland, S. Singh, D.K. McGuire, G.L. Vega, T. Roddy, D.F. Reilly, J. Castro-Perez, J. Kozlitina, P.E. Scherer, Relation of plasma ceramides to visceral adiposity, insulin resistance and the development of type 2 diabetes mellitus: the Dallas Heart Study, Diabetologia 61 (2018) 2570–2579, https://doi.org/10.1007/s00125-018-4720-1.
[76] R.N. Lemaitre, C. Yu, A. Hoofnagle, N. Hari, P. Jensen, A.M. Fretts, J.G. Umans, B. V Howard, C.M. Sitlani, D.S. Siscovick, I.B. King, N. Sotoodehnia, B. Mcknight, Circulating sphingolipids, insulin, HOMA-IR and HOMA-B: the strong heart family study running title: sphingolipids and insulin resistance markers, Diabetes 67 (2018) 1663–1672.
[77] J.M. Haus, S.R. Kashyap, T. Kasumov, R. Zhang, K.R. Kelly, R.A. Defronzo, J. P. Kirwan, Plasma ceramides are elevated in obese subjects with type 2 diabetes and correlate with the severity of insulin resistance, Diabetes 58 (2009) 337–343, https://doi.org/10.2337/db08-1228.
[78] X. Lopez, A.B. Goldfine, W.L. Holland, R. Gordillo, P.E. Scherer, Plasma ceramides are elevated in female children and adolescents with type 2 diabetes, J. Pediatr. Endocrinol. Metab. 26 (2013) 995–998, https://doi.org/10.1515/jpem-2012-0407.
[79] W.L. Holland, J.T. Brozinick, L.P. Wang, E.D. Hawkins, K.M. Sargent, Y. Liu, K. Narra, K.L. Hoehn, T.A. Knotts, A. Siesky, D.H. Nelson, S.K. Karathanasis, G.K. K. Fontenot, M.J. Birnbaum, S.A. Summers, Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance, Cell Metabol. 5 (2007) 167–179, https://doi.org/10.1016/j.cmet.2007.01.002.
[80] R.S. Wright, Recent clinical trials evaluating benefit of drug therapy for modification of HDL cholesterol, Curr. Opin. Cardiol. 28 (2013) 389–398, https://doi.org/10.1097/HCO.0b013e328362059d.

[81] G.D. Smith, G. Hemani, Mendelian randomization: geneticanchorsfor causal inference in epidemiological studies, Hum. Mol. Genet. 23 (2014) 89–98, https://doi.org/10.1093/hmg/ddu328.

[82] M.V. Holmes, F.W. Asselbergs, T.M. Palmer, F. Drenos, M.B. Lanktree, C. P. Nelson, C.E. Dale, S. Padmanabhan, C. Finan, D.I. Swerdlow, V. Tragante, E.P. A. Van Iperen, S. Sivapalaratnam, S. Shah, C.C. Elbers, T. Shah, J. Engmann, C. Giambartolomei, J. White, D. Zabaneh, R. Sofat, S. McLachlan, P. A. Doevendans, A.J. Balmforth, A.S. Hall, K.E. North, B. Almoguera, R. C. Hoogeveen, M. Cushman, M. Fornage, S.R. Patel, S. Redline, D.S. Siscovick, M. Y. Tsai, K.J. Karczewski, M.H. Hofker, W.M. Verschuren, M.L. Bots, Y.T. Van Der Schouw, O. Melander, A.F. Dominiczak, R. Morris, Y. Ben-Shlomo, J. Price, M. Kumari, J. Baumert, A. Peters, B. Thorand, W. Koenig, T.R. Gaunt, S. E. Humphries, R. Clarke, H. Watkins, M. Farrall, J.G. Wilson, S.S. Rich, P.I.W. De Bakker, L.A. Lange, G.D. Smith, A.P. Reiner, P.J. Talmud, M. Kivimäki, D. A. Lawlor, F. Dudbridge, N.J. Samani, B.J. Keating, A.D. Hingorani, J.P. Casas, Mendelian randomization of blood lipids for coronary heart disease, Eur. Heart J. 36 (2015) 539–550, https://doi.org/10.1093/eurheartj/eht571.

[83] S. Burgess, E. Harshfield, 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. 23 (2016) 124–130, https://doi.org/10.1097/MED.0000000000000230.

[84] L.E. Mokry, O. Ahmad, V. Forgetta, G. Thanassoulis, J.B. Richards, Mendelian randomisation applied to drug development in cardiovascular disease: a review, J. Med. Genet. 52 (2015) 71–79, https://doi.org/10.1136/jmedgenet-2014-102438.

[85] B. Keavney, J. Danesh, S. Parish, A. Palmer, S. Clark, L. Youngman, M. Delépine, M. Lathrop, R. Peto, R. Collins, Fibrinogen and coronary heart disease: test of causality by "Mendelian randomization, Int. J. Epidemiol. 35 (2006) 935–943, https://doi.org/10.1093/ije/dyl114.

[86] B.F. Voight, G.M. Peloso, M. Orho-Melander, R. Frikke-Schmidt, M. Barbalic, M. K. Jensen, G. Hindy, H. Holm, E.L. Ding, T. Johnson, H. Schunkert, N.J. Samani, R. Clarke, J.C. Hopewell, J.F. Thompson, M. Li, G. Thorleifsson, C. Newton-Cheh, K. Musunuru, J.P. Pirruccello, D. Saleheen, L. Chen, A.F.R. Stewart, A. Schillert, U. Thorsteinsdottir, G. Thorgeirsson, S. Anand, J.C. Engert, T. Morgan, J. Spertus, M. Stoll, K. Berger, N. Martinelli, D. Girelli, P.P. McKeown, C.C. Patterson, S. E. Epstein, J. Devaney, M.S. Burnett, V. Mooser, S. Ripatti, I. Surakka, M. S. Nieminen, J. Sinisalo, M.L. Lokki, M. Perola, A. Havulinna, U. De Faire, B. Gigante, E. Ingelsson, T. Zeller, P. Wild, P.I.W. De Bakker, O.H. Klungel, A. H. Maitland-Van Der Zee, B.J.M. Peters, A. De Boer, D.E. Grobbee, P. W. Kamphuisen, V.H.M. Deneer, C.C. Elbers, N.C. Onland-Moret, M.H. Hofker, C. Wijmenga, W.M.M. Verschuren, J.M.A. Boer, Y.T. Van Der Schouw, A. Rasheed, P. Frossard, S. Demissie, C. Willer, R. Do, J.M. Ordovas, G. R. Abecasis, M. Boehnke, K.L. Mohlke, M.J. Daly, C. Guiducci, N.P. Burtt, A. Surti, E. Gonzalez, S. Purcell, S. Gabriel, J. Marrugat, J. Peden, J. Erdmann, P. Diemert, C. Willenborg, I.R. Konig, M. Fischer, C. Hengstenberg, A. Ziegler, I. Buysschaert, D. Lambrechts, F. Van De Werf, K.A. Fox, N.E. El Mokhtari, D. Rubin, J. Schrezenmeir, S. Schreiber, A. Schofer, J. Danesh, S. Blankenberg, R. Roberts, R. McPherson, H. Watkins, A.S. Hall, K. Overvad, E. Rimm, E. Boerwinkle, A. Tybjaerg-Hansen, L.A. Cupples, M.P. Reilly, O. Melander, P.M. Mannucci, D. Ardissino, D. Siscovick, R. Elosua, K. Stefansson, C.J. O'Donnell, V. Salomaa, D.J. Rader, L. Peltonen, S.M. Schwartz, D. Altshuler, S. Kathiresan, Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study, Lancet 380 (2012) 572–580, https://doi.org/10.1016/S0140-6736(12)60312-2.

[87] N.J. Timpson, K.H. Wade, G.D. Smith, Mendelian randomization: application to cardiovascular disease, Curr. Hypertens. Rep. 14 (2012) 29–37, https://doi.org/10.1007/s11906-011-0242-7.

[88] N.M. Davies, M.V. Holmes, G. Davey Smith, Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians, BMJ 362 (2018), k601, https://doi.org/10.1136/bmj.k601.

[89] R. Clarke, J.F. Peden, J.C. Hopewell, T. Kyriakou, A. Goel, S.C. Heath, S. Parish, S. Barlera, M.G. Franzosi, S. Rust, D. Bennett, A. Silveira, A. Malarstig, F.R. Green, M. Lathrop, B. Gigante, K. Leander, U. de Faire, U. Seedorf, A. Hamsten, R. Collins, H. Watkins, M. Farrall, Genetic variants associated with Lp(a) lipoprotein level and coronary disease, N. Engl. J. Med. 361 (2009) 2518–2528.

[90] A.A. Hicks, P.P. Pramstaller, A. Johansson, V. Vitart, I. Rudan, P. Ugocsai, Y. Aulchenko, C.S. Franklin, G. Liebisch, J. Erdmann, I. Jonasson, I. V. Zorkoltseva, C. Pattaro, C. Hayward, A. Isaacs, C. Hengstenberg, S. Campbell, C. Gnewuch, A.C.J.W. Janssens, A.V. Kirichenko, I.R. Konig, F. Marroni, O. Polasek, A. Demirkan, I. Kolcic, C. Schwienbacher, W. Igl, Z. Biloglav, J.C. M. Witteman, I. Pichler, G. Zaboli, T.I. Axenovich, A. Peters, S. Schreiber, H. E. Wichmann, H. Schunkert, N. Hastie, B.A. Oostra, S.H. Wild, T. Meitinger, U. Gyllensten, C.M. Van Duijn, J.F. Wilson, A. Wright, G. Schmitz, H. Campbell, Genetic determinants of circulating sphingolipid concentrations in European populations, PLoS Genet. 5 (2009), e1000672, https://doi.org/10.1371/journal.pgen.1000672.

[91] A. Demirkan, C.M. van Duijn, P. Ugocsai, A. Isaacs, P.P. Pramstaller, G. Liebisch, J.F. Wilson, Å. Johansson, I. Rudan, Y.S. Aulchenko, A.V. Kirichenko, A.C.J. W. Janssens, R.C. Jansen, C. Gnewuch, F.S. Domingues, C. Pattaro, S.H. Wild, I. Jonasson, O. Polasek, I.V. Zorkoltseva, A. Hofman, L.C. Karssen, M. Struchalin, J. Floyd, W. Igl, Z. Biloglav, L. Broer, A. Pfeufer, I. Pichler, S. Campbell, G. Zaboli, I. Kolcic, F. Rivadeneira, J. Huffman, N.D. Hastie, A. Uitterlinden, L. Franke, C. S. Franklin, V. Vitart, C.P. Nelson, M. Preuss, J.C. Bis, C.J. O'Donnell, N. Franceschini, J.C.M. Witteman, T. Axenovich, B.A. Oostra, T. Meitinger, A. A. Hicks, C. Hayward, A.F. Wright, U. Gyllensten, H. Campbell, G. Schmitz, Genome-wide association study identifies novel loci associated with circulating phospho- and sphingolipid concentrations, PLoS Genet. 8 (2012), e1002490, https://doi.org/10.1371/journal.pgen.1002490.

[92] R. Tabassum, J.T. Rämö, P. Ripatti, J.T. Koskela, M. Kurki, J. Karjalainen, P. Palta, S. Hassan, J. Nunez-Fontarnau, T.T.J. Kiiskinen, S. Söderlund, N. Matikainen, M.J. Gerl, M.A. Surma, C. Klose, N.O. Stitziel, H. Laivuori, A. S. Havulinna, S.K. Service, V. Salomaa, M. Pirinen, M. Jauhiainen, M.J. Daly, N. B. Freimer, A. Palotie, M.-R. Taskinen, K. Simons, S. Ripatti, Genetic architecture of human plasma lipidome and its link to cardiovascular disease, Nat. Commun. 10 (2019) 4329, https://doi.org/10.1038/s41467-019-11954-8.

[93] K.A. McGurk, S.G. Williams, H. Guo, H. Watkins, M. Farrall, H.J. Cordell, A. Nicolaou, B.D. Keavney, Heritability and family-based GWAS analyses of the N-acyl ethanolamine and ceramide plasma lipidome, Hum. Mol. Genet. ddab002 (2021). https://doi-org.manchester.idm.oclc.org/10.1093/hmg/ddab002.

[94] K.G. Ardlie, D.S. DeLuca, A.V. Segrè, T.J. Sullivan, T.R. Young, E.T. Gelfand, C. A. Trowbridge, J.B. Maller, T. Tukiainen, M. Lek, L.D. Ward, P. Kheradpour, B. Iriarte, Y. Meng, C.D. Palmer, T. Esko, W. Winckler, J.N. Hirschhorn, M. Kellis, D.G. MacArthur, G. Getz, A.A. Shabalin, G. Li, Y.H. Zhou, A.B. Nobel, I. Rusyn, F. A. Wright, T. Lappalainen, P.G. Ferreira, H. Ongen, M.A. Rivas, A. Battle, S. Mostafavi, J. Monlong, M. Sammeth, M. Melé, F. Reverter, J.M. Goldmann, D. Koller, R. Guigó, M.I. McCarthy, E.T. Dermitzakis, E.R. Gamazon, H.K. Im, A. Konkashbaev, D.L. Nicolae, N.J. Cox, T. Flutre, X. Wen, M. Stephens, J. K. Pritchard, Z. Tu, B. Zhang, T. Huang, Q. Long, L. Lin, J. Yang, J. Zhu, J. Liu, A. Brown, B. Mestichelli, D. Tidwell, E. Lo, M. Salvatore, S. Shad, J.A. Thomas, J. T. Lonsdale, M.T. Moser, B.M. Gillard, E. Karasik, K. Ramsey, C. Choi, B.A. Foster, J. Syron, J. Fleming, H. Magazine, R. Hasz, G.D. Walters, J.P. Bridge, M. Miklos, S. Sullivan, L.K. Barker, H.M. Traino, M. Mosavel, L.A. Siminoff, D.R. Valley, D. C. Rohrer, S.D. Jewell, P.A. Branton, L.H. Sobin, M. Barcus, L. Qi, J. McLean, P. Hariharan, K.S. Um, S. Wu, D. Tabor, C. Shive, A.M. Smith, S.A. Buia, A. H. Undale, K.L. Robinson, N. Roche, K.M. Valentino, A. Britton, R. Burges, D. Bradbury, K.W. Hambright, J. Seleski, G.E. Korzeniewski, K. Erickson, Y. Marcus, J. Tejada, M. Taherian, C. Lu, M. Basile, D.C. Mash, S. Volpi, J. P. Struewing, G.F. Temple, J. Boyer, D. Colantuoni, R. Little, S. Koester, L. J. Carithers, H.M. Moore, P. Guan, C. Compton, S.J. Sawyer, J.P. Demchok, J. B. Vaught, C.A. Rabiner, Lockhart, the Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans, Science 384 (2015) 648–660, https://doi.org/10.1126/science.1262110, 80-.

[95] M. Nikpay, A. Goel, H.-H. Won, L.M. Hall, C. Willenborg, S. Kanoni, D. Saleheen, T. Kyriakou, C.P. Nelson, J.C. Hopewell, T.R. Webb, L. Zeng, A. Dehghan, M. Alver, S.M.M. Armasu, K. Auro, A. Bjonnes, D.I. Chasman, S. Chen, I. Ford, N. Franceschini, C. Gieger, C. Grace, S. Gustafsson, J. Huang, S.-J. Hwang, Y. K. Kim, M.E. Kleber, K.W. Lau, X. Lu, Y. Lu, L.-P. Lyytikäinen, E. Mihailov, A. C. Morrison, N. Pervjakova, L. Qu, L.M. Rose, E. Salfati, R. Saxena, M. Scholz, A. V Smith, E. Tikkanen, A. Uitterlinden, X. Yang, W. Zhang, W. Zhao, M. de Andrade, P.S. de Vries, N.R. van Zuydam, S.S. Anand, L. Bertram, F. Beutner, G. Dedoussis, P. Frossard, D. Gauguier, A.H. Goodall, O. Gottesman, M. Haber, B.-G. Han, J. Huang, S. Jalilzadeh, T. Kessler, I.R. König, L. Lannfelt, W. Lieb, L. Lind, C. M. Lindgren, M.-L. Lokki, P.K. Magnusson, N.H. Mallick, N. Mehra, T. Meitinger, F.-R. Memon, A.P. Morris, M.S. Nieminen, N.L. Pedersen, A. Peters, L.S. Rallidis, A. Rasheed, M. Samuel, S.H. Shah, J. Sinisalo, K.E. Stirrups, S. Trompet, L. Wang, K.S. Zaman, D. Ardissino, E. Boerwinkle, I.B. Borecki, E.P. Bottinger, J.E. Buring, J.C. Chambers, R. Collins, L.A. Cupples, J. Danesh, I. Demuth, R. Elosua, S. E. Epstein, T. Esko, M.F. Feitosa, O.H. Franco, M.G. Franzosi, C.B. Granger, D. Gu, V. Gudnason, A.S. Hall, A. Hamsten, T.B. Harris, S.L. Hazen, C. Hengstenberg, A. Hofman, E. Ingelsson, C. Iribarren, J.W. Jukema, P.J. Karhunen, B.-J. Kim, J. S. Kooner, I.J. Kullo, T. Lehtimäki, R.J.F. Loos, O. Melander, A. Metspalu, W. März, C.N. Palmer, M. Perola, T. Quertermous, D.J. Rader, P.M. Ridker, S. Ripatti, R. Roberts, V. Salomaa, D.K. Sanghera, S.M. Schwartz, U. Seedorf, A. F. Stewart, D.J. Stott, J. Thiery, P.A. Zalloua, C.J. O'Donnell, M.P. Reilly, T. L. Assimes, J.R. Thompson, J. Erdmann, R. Clarke, H. Watkins, S. Kathiresan, R. McPherson, P. Deloukas, H. Schunkert, N.J. Samani, M. Farrall, CARDIoGRAMplusC4D Consortium, A comprehensive 1,000 Genomes-based genome-wide association meta-analysis of coronary artery disease, Nat. Genet. 47 (2015) 1121–1130, https://doi.org/10.1038/ng.3396.

[96] N.B. Blackburn, L.F. Michael, P.J. Meikle, J.M. Peralta, M. Mosior, S. McAhren, H. H. Bui, M.A. Bellinger, C. Giles, S. Kumar, A.C. Leandro, M. Almeida, J.M. Weir, M.C. Mahaney, T.D. Dyer, L. Almasy, J.L. VandeBerg, S. Williams-Blangero, D. C. Glahn, R. Duggirala, M. Kowala, J. Blangero, J.E. Curran, Rare DEGS1 variant significantly alters de novo ceramide synthesis pathway, J. Lipid Res. 60 (2019) 1630–1639, https://doi.org/10.1194/jlr.P094433.

[97] C. Bellis, H. Kulkarni, M. Mamtani, J.W. Kent, G. Wong, J.M. Weir, C.K. Barlow, V. Diego, M. Almeida, T.D. Dyer, H.H.H. Göring, L. Almasy, M.C. Mahaney, A. G. Comuzzie, S. Williams-Blangero, P.J. Meikle, J. Blangero, J.E. Curran, Human plasma lipidome is pleiotropically associated with cardiovascular risk factors and death, Circ. Cardiovasc. Genet. 7 (2014) 854–863, https://doi.org/10.1161/CIRCGENETICS.114.000600.

[98] G. Cadby, P.E. Melton, N.S. McCarthy, C. Giles, N.A. Mellett, K. Huynh, J. Hung, J. Beilby, M.-P. Dubé, G.F. Watts, J. Blangero, P.J. Meikle, E.K. Moses, Heritability of 596 lipid species and genetic correlation with cardiovascular traits in the Busselton Family Heart Study, J. Lipid Res. 61 (2020) 537–545, https://doi.org/10.1194/jlr.RA119000594.

[99] M.W.K. Wong, A. Thalamuthu, N. Braidy, K.A. Mather, Y. Liu, L. Ciobanu, B. T. Baune, N.J. Armstrong, J. Kwok, P. Schofield, M.J. Wright, D. Ames, R. Pickford, T. Lee, A. Poljak, P.S. Sachdev, Genetic and environmental determinants of variation in the plasma lipidome of older australian twins, Elife 9 (2020), e58954, https://doi.org/10.7554/eLife.58954.

[100] C.N. Spracklen, P. Chen, Y.J. Kim, X. Wang, H. Cai, S. Li, J. Long, Y. Wu, Y. X. Wang, F. Takeuchi, J.Y. Wu, K.J. Jung, C. Hu, K. Akiyama, Y. Zhang, S. Moon, T.A. Johnson, H. Li, R. Dorajoo, M. He, M.E. Cannon, T.S. Roman, E. Salfati, K. H. Lin, X. Guo, W.H.H. Sheu, D. Absher, L.S. Adair, T.L. Assimes, T. Aung, Q. Cai, L.C. Chang, C.H. Chen, L.H. Chien, L.M. Chuang, S.C. Chuang, S. Du, Q. Fan, C.S. J. Fann, A.B. Feranil, Y. Friedlander, P. Gordon-Larsen, D. Gu, L. Gui, Z. Guo, C. K. Heng, J. Hixson, X. Hou, C.A. Hsiung, Y. Hu, M.Y. Hwang, C.M. Hwu, M. Isono, J.M. Jimmy Juang, C.C. Khor, Y.K. Kim, W.P. Koh, M. Kubo, I. Te Lee, S.J. Lee, W. J. Lee, K.W. Liang, B. Lim, S.H. Lim, J. Liu, T. Nabika, W.H. Pan, H. Peng, T. Quertermous, C. Sabanayagam, K. Sandow, J. Shi, L. Sun, P.C. Tan, S.P. Tan, K. D. Taylor, Y.Y. Teo, S.A. Toh, T. Tsunoda, R.M. van Dam, A. Wang, F. Wang, J. Wang, W. Bin Wei, Y.B. Xiang, J. Yao, J.M. Yuan, R. Zhang, W. Zhao, Y. Der Ida Chen, S.S. Rich, J.I. Rotter, T.D. Wang, T. Wu, X. Lin, B.G. Han, T. Tanaka, Y. S. Cho, T. Katsuya, W. Jia, S.H. Jee, Y.T. Chen, N. Kato, J.B. Jonas, C.Y. Cheng, X. O. Shu, J. He, W. Zheng, T.Y. Wong, W. Huang, B.J. Kim, E.S. Tai, K.L. Mohlke, X. Sim, Association analyses of East Asian individuals and trans-ancestry analyses with European individuals reveal new loci associated with cholesterol and triglyceride levels, Hum. Mol. Genet. 26 (2017) 1770–1784, https://doi.org/10.1093/hmg/ddx062.

[101] C.J. Willer, E.M. Schmidt, S. Sengupta, G.M. Peloso, S. Gustafsson, S. Kanoni, A. Ganna, J. Chen, M.L. Buchkovich, S. Mora, J.S. Beckmann, J.L. Bragg-Gresham, H.Y. Chang, A. Demirkan, H.M. Den Hertog, R. Do, L.A. Donnelly, G.B. Ehret, T. Esko, M.F. Feitosa, T. Ferreira, K. Fischer, P. Fontanillas, R.M. Fraser, D. F. Freitag, D. Gurdasani, K. Heikkilä, E. Hyppönen, A. Isaacs, A.U. Jackson, Å. Johansson, T. Johnson, M. Kaakinen, J. Kettunen, M.E. Kleber, X. Li, J. Luan, L. P. Lyytikäinen, P.K.E. Magnusson, M. Mangino, E. Mihailov, M.E. Montasser, M. Müller-Nurasyid, I.M. Nolte, J.R. O'Connell, C.D. Palmer, M. Perola, A. K. Petersen, S. Sanna, R. Saxena, S.K. Service, S. Shah, D. Shungin, C. Sidore, C. Song, R.J. Strawbridge, I. Surakka, T. Tanaka, T.M. Teslovich, G. Thorleifsson, E.G. Van Den Herik, B.F. Voight, K.A. Volcik, L.L. Waite, A. Wong, Y. Wu, W. Zhang, D. Absher, G. Asiki, I. Barroso, L.F. Been, J.L. Bolton, L.L. Bonnycastle, P. Brambilla, M.S. Burnett, G. Cesana, M. Dimitriou, A.S.F. Doney, A. Döring, P. Elliott, S.E. Epstein, G.I. Eyjolfsson, B. Gigante, M.O. Goodarzi, H. Grallert, M. L. Gravito, C.J. Groves, G. Hallmans, A.L. Hartikainen, C. Hayward, D. Hernandez, A.A. Hicks, H. Holm, Y.J. Hung, T. Illig, M.R. Jones, P. Kaleebu, J. J.P. Kastelein, K.T. Khaw, E. Kim, N. Klopp, P. Komulainen, M. Kumari, C. Langenberg, T. Lehtimäki, S.Y. Lin, J. Lindström, R.J.F. Loos, F. Mach, W. L. McArdle, C. Meisinger, B.D. Mitchell, G. Müller, R. Nagaraja, N. Narisu, T.V. M. Nieminen, R.N. Nsubuga, I. Olafsson, K.K. Ong, A. Palotie, T. Papamarkou, C. Pomilla, A. Pouta, D.J. Rader, M.P. Reilly, P.M. Ridker, F. Rivadeneira, I. Rudan, A. Ruokonen, N. Samani, H. Scharnagl, J. Seeley, K. Silander, A. Stancáková, K. Stirrups, A.J. Swift, L. Tiret, A.G. Uitterlinden, L.J. Van Pelt, S. Vedantam, N. Wainwright, C. Wijmenga, S.H. Wild, G. Willemsen, T. Wilsgaard, J.F. Wilson, E.H. Young, J.H. Zhao, L.S. Adair, D. Arveiler, T. L. Assimes, S. Bandinelli, F. Bennett, M. Bochud, B.O. Boehm, D.I. Boomsma, I. B. Borecki, S.R. Bornstein, P. Bovet, M. Burnier, H. Campbell, A. Chakravarti, J. C. Chambers, Y.D.I. Chen, F.S. Collins, R.S. Cooper, J. Danesh, G. Dedoussis, U. De Faire, A.B. Feranil, J. Ferrières, L. Ferrucci, N.B. Freimer, C. Gieger, L.C. Groop, V. Gudnason, U. Gyllensten, A. Hamsten, T.B. Harris, A. Hingorani, J. N. Hirschhorn, A. Hofman, G.K. Hovingh, C.A. Hsiung, S.E. Humphries, S.C. Hunt, K. Hveem, C. Iribarren, M.R. Järvelin, A. Jula, M. Kähönen, J. Kaprio, A. Kesäniemi, M. Kivimaki, J.S. Kooner, P.J. Koudstaal, R.M. Krauss, D. Kuh, J. Kuusisto, K.O. Kyvik, M. Laakso, T.A. Lakka, L. Lind, C.M. Lindgren, N. G. Martin, W. März, M.I. McCarthy, C.A. McKenzie, P. Meneton, A. Metspalu, L. Moilanen, A.D. Morris, P.B. Munroe, I. Njølstad, N.L. Pedersen, C. Power, P. P. Pramstaller, J.F. Price, B.M. Psaty, T. Quertermous, R. Rauramaa, D. Saleheen, V. Salomaa, D.K. Sanghera, J. Saramies, P.E.H. Schwarz, W.H.H. Sheu, A. R. Shuldiner, A. Siegbahn, T.D. Spector, K. Stefansson, D.P. Strachan, B.O. Tayo, E. Tremoli, J. Tuomilehto, M. Uusitupa, C.M. Van Duijn, P. Vollenweider, L. Wallentin, N.J. Wareham, J.B. Whitfield, B.H.R. Wolffenbuttel, J.M. Ordovas, E. Boerwinkle, C.N.A. Palmer, U. Thorsteinsdottir, D.I. Chasman, J.I. Rotter, P. W. Franks, S. Ripatti, L.A. Cupples, M.S. Sandhu, S.S. Rich, M. Boehnke, P. Deloukas, S. Kathiresan, K.L. Mohlke, E. Ingelsson, G.R. Abecasis, Discovery and refinement of loci associated with lipid levels, Nat. Genet. 45 (2013) 1274–1285, https://doi.org/10.1038/ng.2797.

[102] D. Klarin, S.M. Damrauer, K. Cho, Y.V. Sun, T.M. Teslovich, J. Honerlaw, D. R. Gagnon, S.L. DuVall, J. Li, G.M. Peloso, M. Chaffin, A.M. Small, J. Huang, H. Tang, J.A. Lynch, Y.L. Ho, D.J. Liu, C.A. Emdin, A.H. Li, J.E. Huffman, J.S. Lee, P. Natarajan, R. Chowdhury, D. Saleheen, M. Vujkovic, A. Baras, S. Pyarajan, E. Di Angelantonio, B.M. Neale, A. Naheed, A.V. Khera, J. Danesh, K.M. Chang, G. Abecasis, C. Willer, F.E. Dewey, D.J. Carey, J. Concato, J.M. Gaziano, C. J. O'Donnell, P.S. Tsao, S. Kathiresan, D.J. Rader, P.W.F. Wilson, T.L. Assimes, Genetics of blood lipids among ~300,000 multi-ethnic participants of the Million Veteran Program, Nat. Genet. 50 (2018) 1514–1523, https://doi.org/10.1038/s41588-018-0222-9.

[103] I.E. Christophersen, M. Rienstra, C. Roselli, X. Yin, B. Geelhoed, J. Barnard, H. Lin, D.E. Arking, A. V Smith, C.M. Albert, M. Chaffin, N.R. Tucker, M. Li, D. Klarin, N.A. Bihlmeyer, S.-K. Low, P.E. Weeke, M. Müller-Nurasyid, J.G. Smith, J.A. Brody, M.N. Niemeijer, M. Dörr, S. Trompet, J. Huffman, S. Gustafsson, C. Schurmann, M.E. Kleber, L.-P. Lyytikäinen, I. Seppälä, R. Malik, A.R.V. R. Horimoto, M. Perez, J. Sinisalo, S. Aeschbacher, S. Thériault, J. Yao, F. Radmanesh, S. Weiss, A. Teumer, S.H. Choi, L.-C. Weng, S. Clauss, R. Deo, D. J. Rader, S.H. Shah, A. Sun, J.C. Hopewell, S. Debette, G. Chauhan, Q. Yang, B. B. Worrall, G. Paré, Y. Kamatani, Y.P. Hagemeijer, N. Verweij, J.E. Siland, M. Kubo, J.D. Smith, D.R. Van Wagoner, J.C. Bis, S. Perz, B.M. Psaty, P.M. Ridker, J.W. Magnani, T.B. Harris, L.J. Launer, M.B. Shoemaker, S. Padmanabhan, J. Haessler, T.M. Bartz, M. Waldenberger, P. Lichtner, M. Arendt, J.E. Krieger, M. Kähönen, L. Risch, A.J. Mansur, A. Peters, B.H. Smith, L. Lind, S.A. Scott, Y. Lu, E.B. Bottinger, J. Hernesniemi, C.M. Lindgren, J.A. Wong, J. Huang, M. Eskola, A. P. Morris, I. Ford, A.P. Reiner, G. Delgado, L.Y. Chen, Y.-D.I. Chen, R.K. Sandhu, M. Li, E. Boerwinkle, L. Eisele, L. Lannfelt, N. Rost, C.D. Anderson, K.D. Taylor, A. Campbell, P.K. Magnusson, D. Porteous, L.J. Hocking, E. Vlachopoulou, N. L. Pedersen, K. Nikus, M. Orho-Melander, A. Hamsten, J. Heeringa, J.C. Denny, J. Kriebel, D. Darbar, C. Newton-Cheh, C. Shaffer, P.W. Macfarlane, S. Heilmann-Heimbach, P. Almgren, P.L. Huang, N. Sotoodehnia, E.Z. Soliman, A. G. Uitterlinden, A. Hofman, O.H. Franco, U. Völker, K.-H. Jöckel, M.F. Sinner, H. J. Lin, X. Guo, M. Dichgans, E. Ingelsson, C. Kooperberg, O. Melander, R.J.F. Loos, J. Laurikka, D. Conen, J. Rosand, P. van der Harst, M.-L. Lokki, S. Kathiresan, A. Pereira, J.W. Jukema, C. Hayward, J.I. Rotter, W. März, T. Lehtimäki, B. H. Stricker, M.K. Chung, S.B. Felix, V. Gudnason, A. Alonso, D.M. Roden, S. Kääb, D.I. Chasman, S.R. Heckbert, E.J. Benjamin, T. Tanaka, K.L. Lunetta, S.A. Lubitz, P.T. Ellinor, Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation, Nat. Genet. 49 (2017) 946–952, https://doi.org/10.1038/ng.3843.

[104] J.B. Nielsen, R.B. Thorolfsdottir, L.G. Fritsche, W. Zhou, M.W. Skov, S.E. Graham, T.J. Herron, S. McCarthy, E.M. Schmidt, G. Sveinbjornsson, I. Surakka, M. R. Mathis, M. Yamazaki, R.D. Crawford, M.E. Gabrielsen, A.H. Skogholt, O. L. Holmen, M. Lin, B.N. Wolford, R. Dey, H. Dalen, P. Sulem, J.H. Chung, J. D. Backman, D.O. Arnar, U. Thorsteinsdottir, A. Baras, C. O'Dushlaine, A.G. Holst, X. Wen, W. Hornsby, F.E. Dewey, M. Boehnke, S. Kheterpal, B. Mukherjee, S. Lee, H.M. Kang, H. Holm, J. Kitzman, J.A. Shavit, J. Jalife, C.M. Brummett, T. M. Teslovich, D.J. Carey, D.F. Gudbjartsson, K. Stefansson, G.R. Abecasis, K. Hveem, C.J. Willer, Biobank-driven genomic discovery yields new insight into atrial fibrillation biology, Nat. Genet. 50 (2018) 1225–1233, https://doi.org/10.1038/s41588-018-0171-3.

[105] C. Roselli, M.D. Chaffin, L.C. Weng, S. Aeschbacher, G. Ahlberg, C.M. Albert, P. Almgren, A. Alonso, C.D. Anderson, K.G. Aragam, D.E. Arking, J. Barnard, T. M. Bartz, E.J. Benjamin, N.A. Bihlmeyer, J.C. Bis, H.L. Bloom, E. Boerwinkle, E. B. Bottinger, J.A. Brody, H. Calkins, A. Campbell, T.P. Cappola, J. Carlquist, D. I. Chasman, L.Y. Chen, Y.D.I. Chen, E.K. Choi, S.H. Choi, I.E. Christophersen, M. K. Chung, J.W. Cole, D. Conen, J. Cook, H.J. Crijns, M.J. Cutler, S.M. Damrauer, B.R. Daniels, D. Darbar, G. Delgado, J.C. Denny, M. Dichgans, M. Dörr, E. A. Dudink, S.C. Dudley, N. Esa, T. Esko, M. Eskola, D. Fatkin, S.B. Felix, I. Ford, O. H. Franco, B. Geelhoed, R.P. Grewal, V. Gudnason, X. Guo, N. Gupta, S. Gustafsson, R. Gutmann, A. Hamsten, T.B. Harris, C. Hayward, S.R. Heckbert, J. Hernesniemi, L.J. Hocking, A. Hofman, A.R.V.R. Horimoto, J. Huang, P. L. Huang, J. Huffman, E. Ingelsson, E.G. Ipek, K. Ito, J. Jimenez-Conde, R. Johnson, J.W. Jukema, S. Kääb, M. Kähönen, Y. Kamatani, J.P. Kane, A. Kastrati, S. Kathiresan, P. Katschnig-Winter, M. Kavousi, T. Kessler, B. L. Kietselaer, P. Kirchhof, M.E. Kleber, S. Knight, J.E. Krieger, M. Kubo, L. J. Launer, J. Laurikka, T. Lehtimäki, K. Leineweber, R.N. Lemaitre, M. Li, H. E. Lim, H.J. Lin, H. Lin, L. Lind, C.M. Lindgren, M.L. Lokki, B. London, R.J.F. Loos, S.K. Low, Y. Lu, L.P. Lyytikäinen, P.W. Macfarlane, P.K. Magnusson, A. Mahajan, R. Malik, A.J. Mansur, G.M. Marcus, L. Margolin, K.B. Margulies, W. März, D. D. McManus, O. Melander, S. Mohanty, J.A. Montgomery, M.P. Morley, A. P. Morris, M. Müller-Nurasyid, A. Natale, S. Nazarian, B. Neumann, C. Newton-Cheh, M.N. Niemeijer, K. Nikus, P. Nilsson, R. Noordam, H. Oellers, M.S. Olesen, M. Orho-Melander, S. Padmanabhan, H.N. Pak, G. Paré, N.L. Pedersen, J. Pera, A. Pereira, D. Porteous, B.M. Psaty, S.L. Pulit, C.R. Pullinger, D.J. Rader, L. Refsgaard, M. Ribasés, P.M. Ridker, M. Rienstra, L. Risch, D.M. Roden, J. Rosand, M.A. Rosenberg, N. Rost, J.I. Rotter, S. Saba, R.K. Sandhu, R. B. Schnabel, K. Schramm, H. Schunkert, C. Schurman, S.A. Scott, I. Seppälä, C. Shaffer, S. Shah, A.A. Shalaby, J. Shim, M.B. Shoemaker, J.E. Siland, J. Sinisalo, M.F. Sinner, A. Slowik, A.V. Smith, B.H. Smith, J.G. Smith, J.D. Smith, N.L. Smith, E.Z. Soliman, N. Sotoodehnia, B.H. Stricker, A. Sun, H. Sun, J. H. Svendsen, T. Tanaka, K. Tanriverdi, K.D. Taylor, M. Teder-Laving, A. Teumer, S. Thériault, S. Trompet, N.R. Tucker, A. Tveit, A.G. Uitterlinden, P. van der Harst, I.C. van Gelder, D.R. van Wagoner, N. Verweij, E. Vlachopoulou, U. Völker, B. Wang, P.E. Weeke, B. Weijs, R. Weiss, S. Weiss, Q.S. Wells, K.L. Wiggins, J. A. Wong, D. Woo, B.B. Worrall, P.S. Yang, J. Yao, Z.T. Yoneda, T. Zeller, L. Zeng,

S.A. Lubitz, K.L. Lunetta, P.T. Ellinor, Multi-ethnic genome-wide association study for atrial fibrillation, Nat. Genet. 50 (2018) 1225–1233, https://doi.org/10.1038/s41588-018-0133-9.

[106] S. Gizurarson, M. Ståhlman, A. Jeppsson, Y. Shao, B. Redfors, L. Bergfeldt, J. Borén, E. Omerovic, Atrial fibrillation in patients admitted to coronary care units in western Sweden - focus on obesity and lipotoxicity, J. Electrocardiol. 48 (2015) 853–860, https://doi.org/10.1016/j.jelectrocard.2014.12.010.

[107] C.N. Spracklen, M. Horikoshi, Y.J. Kim, K. Lin, F. Bragg, S. Moon, K. Suzuki, C.H. T. Tam, Y. Tabara, S.H. Kwak, F. Takeuchi, J. Long, V.J.Y. Lim, J.F. Chai, C. H. Chen, M. Nakatochi, J. Yao, H.S. Choi, A.K. Iyengar, H.J. Perrin, S.M. Brotman, M. van de Bunt, A.L. Gloyn, J.E. Below, M. Boehnke, D.W. Bowden, J. C. Chambers, A. Mahajan, M.I. McCarthy, M.C.Y. Ng, L.E. Petty, W. Zhang, A. P. Morris, L.S. Adair, M. Akiyama, Z. Bian, J.C.N. Chan, L.C. Chang, M.L. Chee, Y. D.I. Chen, Y.T. Chen, Z. Chen, L.M. Chuang, S. Du, P. Gordon-Larsen, M. Gross, X. Guo, Y. Guo, S. Han, A.G. Howard, W. Huang, Y.J. Hung, M.Y. Hwang, C. M. Hwu, S. Ichihara, M. Isono, H.M. Jang, G. Jiang, J.B. Jonas, Y. Kamatani, T. Katsuya, T. Kawaguchi, C.C. Khor, K. Kohara, M.S. Lee, N.R. Lee, L. Li, J. Liu, A. O. Luk, J. Lv, Y. Okada, M.A. Pereira, C. Sabanayagam, J. Shi, D.M. Shin, W.Y. So, A. Takahashi, B. Tomlinson, F.J. Tsai, R.M. van Dam, Y.B. Xiang, K. Yamamoto, T. Yamauchi, K. Yoon, C. Yu, J.M. Yuan, L. Zhang, W. Zheng, M. Igase, Y.S. Cho, J. I. Rotter, Y.X. Wang, W.H.H. Sheu, M. Yokota, J.Y. Wu, C.Y. Cheng, T.Y. Wong, X. O. Shu, N. Kato, K.S. Park, E.S. Tai, F. Matsuda, W.P. Koh, R.C.W. Ma, S. Maeda, I. Y. Millwood, J. Lee, T. Kadowaki, R.G. Walters, B.J. Kim, K.L. Mohlke, X. Sim, Identification of type 2 diabetes loci in 433,540 East Asian individuals, Nature 582 (2020) 240–245, https://doi.org/10.1038/s41586-020-2263-3.

[108] M. Fenger, A. Linneberg, J. Jeppesen, Network-based analysis of the sphingolipid metabolism in hypertension, Front. Genet. 5 (2015) 1–14, https://doi.org/10.3389/fgene.2015.00084.

[109] A.S. Havulinna, M. Sysi-Aho, M. Hilvo, D. Kauhanen, R. Hurme, K. Ekroos, V. Salomaa, R. Laaksonen, Circulating ceramides predict cardiovascular outcomes in the population-based FINRISK 2002 cohort, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 2424–2430, https://doi.org/10.1161/ATVBAHA.116.307497.

[110] J. Yu, W. Pan, R. Shi, T. Yang, Y. Li, G. Yu, Y. Bai, E.H. Schuchman, X. He, G. Zhang, Ceramide is upregulated and associated with mortality in patients with chronic heart failure, Can. J. Cardiol. 31 (2015) 357–363, https://doi.org/10.1016/j.cjca.2014.12.007.

[111] L.P. de Carvalho, S.H. Tan, G.S. Ow, Z. Tang, J. Ching, J.P. Kovalik, S.C. Poh, C. T. Chin, A.M. Richards, E.C. Martinez, R.W. Troughton, A.Y.Y. Fong, B.P. Yan, A. Seneviratna, V. Sorokin, S.A. Summers, V.A. Kuznetsov, M.Y. Chan, Plasma ceramides as prognostic biomarkers and their arterial and myocardial tissue correlates in acute myocardial infarction, JACC basic to transl, Science 3 (2018) 163–175, https://doi.org/10.1016/j.jacbts.2017.12.005.

[112] E. Wheeler, A. Leong, C.T. Liu, M.F. Hivert, R.J. Strawbridge, C. Podmore, M. Li, J. Yao, X. Sim, J. Hong, A.Y. Chu, W. Zhang, X. Wang, P. Chen, N.M. Maruthur, B. C. Porneala, S.J. Sharp, Y. Jia, E.K. Kabagambe, L.C. Chang, W.M. Chen, C.E. Elks, D.S. Evans, Q. Fan, F. Giulianini, M.J. Go, J.J. Hottenga, Y. Hu, A.U. Jackson, S. Kanoni, Y.J. Kim, M.E. Kleber, C. Ladenvall, C. Lecoeur, S.H. Lim, Y. Lu, A. Mahajan, C. Marzi, M.A. Nalls, P. Navarro, I.M. Nolte, L.M. Rose, D.V. Rybin, S. Sanna, Y. Shi, D.O. Stram, F. Takeuchi, S.P. Tan, P.J. van der Most, J.V. Van Vliet-Ostaptchouk, A. Wong, L. Yengo, W. Zhao, A. Goel, M.T. Martinez Larrad, D. Radke, P. Salo, T. Tanaka, E.P.A. van Iperen, G. Abecasis, S. Afaq, B. Z. Alizadeh, A.G. Bertoni, A. Bonnefond, Y. Böttcher, E.P. Bottinger, H. Campbell, O.D. Carlson, C.H. Chen, Y.S. Cho, W.T. Garvey, C. Gieger, M.O. Goodarzi, H. Grallert, A. Hamsten, C.A. Hartman, C. Herder, C.A. Hsiung, J. Huang, M. Igase, M. Isono, T. Katsuya, C.C. Khor, W. Kiess, K. Kohara, P. Kovacs, J. Lee, W.J. Lee, B. Lehne, H. Li, J. Liu, S. Lobbens, J. Luan, V. Lyssenko, T. Meitinger, T. Miki, I. Miljkovic, S. Moon, A. Mulas, G. Müller, M. Müller-Nurasyid, R. Nagaraja, M. Nauck, J.S. Pankow, O. Polasek, I. Prokopenko, P.S. Ramos, L. Rasmussen-Torvik, W. Rathmann, S.S. Rich, N.R. Robertson, M. Roden, R. Roussel, I. Rudan, R.A. Scott, W.R. Scott, B. Sennblad, D.S. Siscovick, K. Strauch, L. Sun, M. Swertz, S.M. Tajuddin, K.D. Taylor, Y.Y. Teo, Y.C. Tham, A. Tönjes, N.J. Wareham, G. Willemsen, T. Wilsgaard, A.D. Hingorani, J. Egan, L. Ferrucci, G.K. Hovingh, A. Jula, M. Kivimaki, M. Kumari, I. Njølstad, C.N. A. Palmer, M. Serrano Ríos, M. Stumvoll, H. Watkins, T. Aung, M. Blüher, M. Boehnke, D.I. Boomsma, S.R. Bornstein, J.C. Chambers, D.I. Chasman, Y.D. I. Chen, Y.T. Chen, C.Y. Cheng, F. Cucca, E.J.C. de Geus, P. Deloukas, M.K. Evans, M. Fornage, Y. Friedlander, P. Froguel, L. Groop, M.D. Gross, T.B. Harris, C. Hayward, C.K. Heng, E. Ingelsson, N. Kato, B.J. Kim, W.P. Koh, J.S. Kooner, A. Körner, D. Kuh, J. Kuusisto, M. Laakso, X. Lin, Y. Liu, R.J.F. Loos, P.K. E. Magnusson, W. März, M.I. McCarthy, A.J. Oldehinkel, K.K. Ong, N.L. Pedersen, M.A. Pereira, A. Peters, P.M. Ridker, C. Sabanayagam, M. Sale, D. Saleheen, J. Saltevo, P.E.H. Schwarz, W.H.H. Sheu, H. Snieder, T.D. Spector, Y. Tabara, J. Tuomilehto, R.M. van Dam, J.G. Wilson, J.F. Wilson, B.H.R. Wolffenbuttel, T. Y. Wong, J.Y. Wu, J.M. Yuan, A.B. Zonderman, N. Soranzo, X. Guo, D.J. Roberts, J.C. Florez, R. Sladek, J. Dupuis, A.P. Morris, E.S. Tai, E. Selvin, J.I. Rotter, C. Langenberg, I. Barroso, J.B. Meigs, Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: a transethnic genome-wide meta-analysis, PLoS Med. 14 (2017), https://doi.org/10.1371/journal.pmed.1002383.

[113] M. Gorski, P.J. van der Most, A. Teumer, A.Y. Chu, M. Li, V. Mijatovic, I.M. Nolte, M. Cocca, D. Taliun, F. Gomez, Y. Li, B. Tayo, A. Tin, M.F. Feitosa, T. Aspelund, J. Attia, R. Biffar, M. Bochud, E. Boerwinkle, I. Borecki, E.P. Bottinger, M.-H. Chen, V. Chouraki, M. Ciullo, J. Coresh, M.C. Cornelis, G.C. Curhan, A. P. d'Adamo, A. Dehghan, L. Dengler, J. Ding, G. Eiriksdottir, K. Endlich, S. Enroth, T. Esko, O.H. Franco, P. Gasparini, C. Gieger, G. Girotto, O. Gottesman, V. Gudnason, U. Gyllensten, S.J. Hancock, T.B. Harris, C. Helmer, S. Höllerer, E. Hofer, A. Hofman, E.G. Holliday, G. Homuth, F.B. Hu, C. Huth, N. Hutri-Kähönen, S.-J. Hwang, M. Imboden, Å. Johansson, M. Kähönen, W. König, H. Kramer, B.K. Krämer, A. Kumar, Z. Kutalik, J.-C. Lambert, L.J. Launer, T. Lehtimäki, M. de Borst, G. Navis, M. Swertz, Y. Liu, K. Lohman, R.J.F. Loos, Y. Lu, L.-P. Lyytikäinen, M.A. McEvoy, C. Meisinger, T. Meitinger, A. Metspalu, M. Metzger, E. Mihailov, P. Mitchell, M. Nauck, A.J. Oldehinkel, M. Olden, B. Wjh Penninx, G. Pistis, P.P. Pramstaller, N. Probst-Hensch, O.T. Raitakari, R. Rettig, P. M. Ridker, F. Rivadeneira, A. Robino, S.E. Rosas, D. Ruderfer, D. Ruggiero, Y. Saba, C. Sala, H. Schmidt, R. Schmidt, R.J. Scott, S. Sedaghat, A.V. Smith, R. Sorice, B. Stengel, S. Stracke, K. Strauch, D. Toniolo, A.G. Uitterlinden, S. Ulivi, J.S. Viikari, U. Völker, P. Vollenweider, H. Völzke, D. Vuckovic, M. Waldenberger, J. Jin Wang, Q. Yang, D.I. Chasman, G. Tromp, H. Snieder, I.M. Heid, C.S. Fox, A. Köttgen, C. Pattaro, C.A. Böger, C. Fuchsberger, 1000 Genomes-based meta-analysis identifies 10 novel loci for kidney function, Sci. Rep. 7 (2017) 45040, https://doi.org/10.1038/srep45040.

[114] A.P. Morris, T.H. Le, H. Wu, A. Akbarov, P.J. van der Most, G. Hemani, G. D. Smith, A. Mahajan, K.J. Gaulton, G.N. Nadkarni, A. Valladares-Salgado, N. Wacher-Rodarte, J.C. Mychaleckyj, N.D. Dueker, X. Guo, Y. Hai, J. Haessler, Y. Kamatani, A.M. Stilp, G. Zhu, J.P. Cook, J. Ärnlöv, S.H. Blanton, M.H. de Borst, E.P. Bottinger, T.A. Buchanan, S. Cechova, F.J. Charchar, P.L. Chu, J. Damman, J. Eales, A.G. Gharavi, V. Giedraitis, A.C. Heath, E. Ipp, K. Kiryluk, H.J. Kramer, M. Kubo, A. Larsson, C.M. Lindgren, Y. Lu, P.A.F. Madden, G.W. Montgomery, G. J. Papanicolaou, L.J. Raffel, R.L. Sacco, E. Sanchez, H. Stark, J. Sundstrom, K. D. Taylor, A.H. Xiang, A. Zivkovic, L. Lind, E. Ingelsson, N.G. Martin, J. B. Whitfield, J. Cai, C.C. Laurie, Y. Okada, K. Matsuda, C. Kooperberg, Y.D. I. Chen, T. Rundek, S.S. Rich, R.J.F. Loos, E.J. Parra, M. Cruz, J.I. Rotter, H. Snieder, M. Tomaszewski, B.D. Humphreys, N. Franceschini, Trans-ethnic kidney function association study reveals putative causal genes and effects on kidney-specific disease aetiologies, Nat. Commun. 10 (2019) 29, https://doi.org/10.1038/s41467-018-07867-7.

[115] T.G. Richardson, E. Sanderson, T.M. Palmerid, M.A. Korpelaid, B.A. Ference, G. D. Smith, M.V. Holmes, Evaluating the relationship between circulating lipoprotein lipids and apolipoproteins with risk of coronary heart disease: a multivariable Mendelian randomisation analysis, PLoS Med. 17 (2020), e1003062, https://doi.org/10.1371/journal.pmed.1003062.

[116] P. Costa-Urrutia, V. Colistro, A.S. Jiménez-Osorio, H. Cárdenas-Hernández, J. Solares-Tlapechco, M. Ramirez-Alcántara, J. Granados, I. de J. Ascencio-Montiel, M.E. Rodríguez-Arellano, Genome-wide association study of body mass index and body fat in mexican-mestizo children, Genes 10 (2019) 945, https://doi.org/10.3390/genes10110945.

[117] L.V. Wain, A. Vaez, R. Jansen, R. Joehanes, P.J. Van Der Most, A. M. Erzurumluoglu, P.F. O'Reilly, C.P. Cabrera, H.R. Warren, L.M. Rose, G. C. Verwoert, J.J. Hottenga, R.J. Strawbridge, T. Esko, D.E. Arking, S.J. Hwang, X. Guo, Z. Kutalik, S. Trompet, N. Shrine, A. Teumer, J.S. Ried, J.C. Bis, A. V. Smith, N. Amin, I.M. Nolte, L.P. Lyytikäinen, A. Mahajan, N.J. Wareham, E. Hofer, P.K. Joshi, K. Kristiansson, M. Traglia, A.S. Havulinna, A. Goel, M. A. Nalls, S. Sõber, D. Vuckovic, J. Luan, F.M. Del Greco, K.L. Ayers, J. Marrugat, D. Ruggiero, L.M. Lopez, T. Niiranen, S. Enroth, A.U. Jackson, C.P. Nelson, J. E. Huffman, W. Zhang, J. Marten, I. Gandin, S.E. Harris, T. Zemunik, Y. Lu, E. Evangelou, N. Shah, M.H. De Borst, M. Mangino, B.P. Prins, A. Campbell, R. Li-Gao, G. Chauhan, C. Oldmeadow, G. Abecasis, M. Abedi, C.M. Barbieri, M. R. Barnes, C. Batini, J. Beilby, T. Blake, M. Boehnke, E.P. Bottinger, P.S. Braund, M. Brown, M. Brumat, H. Campbell, J.C. Chambers, M. Cocca, F. Collins, J. Connell, H.J. Cordell, J.J. Damman, G. Davies, E.J. De Geus, R. De Mutsert, J. Deelen, Y. Demirkale, A.S.F. Doney, M. Dörr, M. Farrall, T. Ferreira, M. Frånberg, H. Gao, V. Giedraitis, C. Gieger, F. Giulianini, A.J. Gow, A. Hamsten, T.B. Harris, A. Hofman, E.G. Holliday, J. Hui, M.R. Jarvelin, Å. Johansson, A. D. Johnson, P. Jousilahti, A. Jula, M. Kähönen, S. Kathiresan, K.T. Khaw, I. Kolcic, S. Koskinen, C. Langenberg, M. Larson, L.J. Launer, B. Lehne, D.C.M. Liewald, L. Lin, L. Lind, F. Mach, C. Mamasoula, C. Menni, B. Mifsud, Y. Milaneschi, A. Morgan, A.D. Morris, A.C. Morrison, P.J. Munson, P. Nandakumar, Q. T. Nguyen, T. Nutile, A.J. Oldehinkel, B.A. Oostra, E. Org, S. Padmanabhan, A. Palotie, G. Paré, A. Pattie, B.W.J.H. Penninx, N. Poulter, P.P. Pramstaller, O. T. Raitakari, M. Ren, K. Rice, P.M. Ridker, H. Riese, S. Ripatti, A. Robino, J. I. Rotter, I. Rudan, Y. Saba, A. Saint Pierre, C.F. Sala, A.P. Sarin, R. Schmidt, R. Scott, M.A. Seelen, D.C. Shields, D. Siscovick, R. Sorice, A. Stanton, D.J. Stott, J. Sundström, M. Swertz, K.D. Taylor, S. Thom, I. Tzoulaki, C. Tzourio, A. G. Uitterlinden, U. Völker, P. Vollenweider, S. Wild, G. Willemsen, A.F. Wright, J. Yao, S. Thériault, D. Conen, J. Attia, P. Sever, S. Debette, D.O. Mook-Kanamori, E. Zeggini, T.D. Spector, P. Van Der Harst, C.N.A. Palmer, A.C. Vergnaud, R.J. F. Loos, O. Polasek, J.M. Starr, G. Girotto, C. Hayward, J.S. Kooner, C. M. Lindgren, V. Vitart, N.J. Samani, J. Tuomilehto, U. Gyllensten, P. Knekt, I. J. Deary, M. Ciullo, R. Elosua, B.D. Keavney, A.A. Hicks, R.A. Scott, P. Gasparini,

M. Laan, Y. Liu, H. Watkins, C.A. Hartman, V. Salomaa, D. Toniolo, M. Perola, J. F. Wilson, H. Schmidt, J.H. Zhao, T. Lehtimäki, C.M. Van Duijn, V. Gudnason, B. M. Psaty, A. Peters, R. Rettig, A. James, J.W. Jukema, D.P. Strachan, W. Palmas, A. Metspalu, E. Ingelsson, D.I. Boomsma, O.H. Franco, M. Bochud, C. Newton-Cheh, P.B. Munroe, P. Elliott, D.I. Chasman, A. Chakravarti, J. Knight, A. P. Morris, D. Levy, M.D. Tobin, H. Snieder, M.J. Caulfield, G.B. Ehret, Novel blood pressure locus and gene discovery using genome-wide association study and expression data sets from blood and the kidney, Hypertension 70 (2017) e4–e19, https://doi.org/10.1161/HYPERTENSIONAHA.117.09438.

[118] C. Liu, A.T. Kraja, J.A. Smith, J.A. Brody, N. Franceschini, J.C. Bis, K. Rice, A. C. Morrison, Y. Lu, S. Weiss, X. Guo, W. Palmas, L.W. Martin, Y.D.I. Chen, P. Surendran, F. Drenos, J.P. Cook, P.L. Auer, A.Y. Chu, A. Giri, W. Zhao, J. Jakobsdottir, L.A. Lin, J.M. Stafford, N. Amin, H. Mei, J. Yao, A. Voorman, M. G. Larson, M.L. Grove, A.V. Smith, S.J. Hwang, H. Chen, T. Huan, G. Kosova, N. O. Stitziel, S. Kathiresan, N. Samani, H. Schunkert, P. Deloukas, M. Li, C. Fuchsberger, C. Pattaro, M. Gorski, C. Kooperberg, G.J. Papanicolaou, J. E. Rossouw, J.D. Faul, S.L.R. Kardia, C. Bouchard, L.J. Raffel, A.G. Uitterlinden, O.H. Franco, R.S. Vasan, C.J. O'Donnell, K.D. Taylor, K. Liu, E.P. Bottinger, O. Gottesman, E.W. Daw, F. Giulianini, S. Ganesh, E. Salfati, T.B. Harris, L. J. Launer, M. Dörr, S.B. Felix, R. Rettig, H. Völzke, E. Kim, W.J. Lee, I. Te Lee, W. H.H. Sheu, K.S. Tsosie, D.R.V. Edwards, Y. Liu, A. Correa, D.R. Weir, U. Völker, P. M. Ridker, E. Boerwinkle, V. Gudnason, A.P. Reiner, C.M. Van Duijn, I.B. Borecki, T.L. Edwards, A. Chakravarti, J.I. Rotter, B.M. Psaty, R.J.F. Loos, M. Fornage, G. B. Ehret, C. Newton-Cheh, D. Levy, D.I. Chasman, Meta-analysis identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci, Nat. Genet. 48 (2016) 1162–1170, https://doi.org/10.1038/ng.3660.

[119] P. Surendran, F. Drenos, R. Young, H. Warren, J.P. Cook, A.K. Manning, N. Grarup, X. Sim, D.R. Barnes, K. Witkowska, J.R. Staley, V. Tragante, T. Tukiainen, H. Yaghootkar, N. Masca, D.F. Freitag, T. Ferreira, O. Giannakopoulou, A. Tinker, M. Harakalova, E. Mihailov, C. Liu, A.T. Kraja, S. F. Nielsen, A. Rasheed, M. Samuel, W. Zhao, L.L. Bonnycastle, A.U. Jackson, N. Narisu, A.J. Swift, L. Southam, J. Marten, J.R. Huyghe, A. Stančáková, C. Fava, T. Ohlsson, A. Matchan, K.E. Stirrups, J. Bork-Jensen, A.P. Gjesing, J. Kontto, M. Perola, S. Shaw-Hawkins, A.S. Havulinna, H. Zhang, L.A. Donnelly, C. J. Groves, N.W. Rayner, M.J. Neville, N.R. Robertson, A.M. Yiorkas, K.H. Herzig, E. Kajantie, W. Zhang, S.M. Willems, L. Lannfelt, G. Malerba, N. Soranzo, E. Trabetti, N. Verweij, E. Evangelou, A. Moayyeri, A.C. Vergnaud, C.P. Nelson, A. Poveda, T.V. Varga, M. Caslake, A.J.M. De Craen, S. Trompet, J. Luan, R. A. Scott, S.E. Harris, D.C.M. Liewald, R. Marioni, C. Menni, A.E. Farmaki, G. Hallmans, F. Renström, J.E. Huffman, M. Hassinen, S. Burgess, R.S. Vasan, J. F. Felix, M. Uria-Nickelsen, A. Malarstig, D.F. Reilly, M. Hoek, T.F. Vogt, H. Lin, W. Lieb, M. Traylor, H.S. Markus, H.M. Highland, A.E. Justice, E. Marouli, J. Lindström, M. Uusitupa, P. Komulainen, T.A. Lakka, R. Rauramaa, O. Polasek, I. Rudan, O. Rolandsson, P.W. Franks, G. Dedoussis, T.D. Spector, P. Jousilahti, S. Männistö, I.J. Deary, J.M. Starr, C. Langenberg, N.J. Wareham, M.J. Brown, A. F. Dominiczak, J.M. Connell, J.W. Jukema, N. Sattar, I. Ford, C.J. Packard, T. Esko, R. Mägi, A. Metspalu, R.A. De Boer, P. Van Der Meer, P. Van Der Harst, G. Gambaro, E. Ingelsson, L. Lind, P.I.W. De Bakker, M.E. Numans, I. Brandslund, C. Christensen, E.R.B. Petersen, E. Korpi-Hyövälti, H. Oksa, J.C. Chambers, J. S. Kooner, A.I.F. Blakemore, S. Franks, M.R. Jarvelin, L.L. Husemoen, A. Linneberg, T. Skaaby, B. Thuesen, F. Karpe, J. Tuomilehto, A.S.F. Doney, A. D. Morris, C.N.A. Palmer, O.L. Holmen, K. Hveem, C.J. Willer, T. Tuomi, L. Groop, A. Käräjämäki, A. Palotie, S. Ripatti, V. Salomaa, D.S. Alam, A.A.S. Majumder, E. Di Angelantonio, R. Chowdhury, M.I. McCarthy, N. Poulter, A.V. Stanton, P. Sever, P. Amouyel, D. Arveiler, S. Blankenberg, J. Ferrières, F. Kee, K. Kuulasmaa, M. Müller-Nurasyid, G. Veronesi, J. Virtamo, P. Deloukas, P. Elliott, E. Zeggini, S. Kathiresan, O. Melander, J. Kuusisto, M. Laakso, S. Padmanabhan, D.J. Porteous, C. Hayward, G. Scotland, F.S. Collins, K. L. Mohlke, T. Hansen, O. Pedersen, M. Boehnke, H.M. Stringham, P. Frossard, C. Newton-Cheh, M.D. Tobin, B.G. Nordestgaard, M.J. Caulfield, A. Mahajan, A. P. Morris, M. Tomaszewski, N.J. Samani, D. Saleheen, F.W. Asselbergs, C. M. Lindgren, J. Danesh, L.V. Wain, A.S. Butterworth, J.M.M. Howson, P. B. Munroe, Trans-ancestry meta-analyses identify rare and common variants associated with blood pressure and hypertension, Nat. Genet. 48 (2016) 1151–1161, https://doi.org/10.1038/ng.3654.

[120] P.S. De Vries, M.R. Brown, A.R. Bentley, Y.J. Sung, T.W. Winkler, I. Ntalla, K. Schwander, A.T. Kraja, X. Guo, N. Franceschini, C.Y. Cheng, X. Sim, D. Vojinovic, J.E. Huffman, S.K. Musani, C. Li, M.F. Feitosa, M.A. Richard, R. Noordam, H. Aschard, T.M. Bartz, L.F. Bielak, X. Deng, R. Dorajoo, K. K. Lohman, A.K. Manning, T. Rankinen, A.V. Smith, S.M. Tajuddin, E. Evangelou, M. Graff, M. Alver, M. Boissel, J.F. Chai, X. Chen, J. Divers, I. Gandin, C. Gao, A. Goel, Y. Hagemeijer, S.E. Harris, F.P. Hartwig, M. He, A.R.V.R. Horimoto, F. C. Hsu, A.U. Jackson, A. Kasturiratne, P. Komulainen, B. Kühnel, F. Laguzzi, J. H. Lee, J. Luan, L.P. Lyytikäinen, N. Matoba, I.M. Nolte, M. Pietzner, M. Riaz, M. A. Said, R.A. Scott, T. Sofer, A. Stančáková, F. Takeuchi, B.O. Tayo, P.J. Van Der Most, T.V. Varga, Y. Wang, E.B. Ware, W. Wen, L.R. Yanek, W. Zhang, J.H. Zhao, S. Afaq, N. Amin, M. Amini, D.E. Arking, T. Aung, C. Ballantyne, E. Boerwinkle, U. Broeckel, A. Campbell, M. Canouil, S. Charumathi, Y.D.I. Chen, J.M. Connell, U. De Faire, L. De Las Fuentes, R. De Mutsert, H.J. De Silva, J. Ding, A. F. Dominiczak, Q. Duan, C.B. Eaton, R.N. Eppinga, J.D. Faul, V. Fisher, T. Forrester, O.H. Franco, Y. Friedlander, M. Ghanbari, F. Giulianini, H.J. Grabe, M.L. Grove, C.C. Gu, T.B. Harris, S. Heikkinen, C.K. Heng, M. Hirata, J.E. Hixson, B.V. Howard, M.A. Ikram, D.R. Jacobs, C. Johnson, J.B. Jonas, C.M. Kammerer, T. Katsuya, C.C. Khor, T.O. Kilpeläinen, W.P. Koh, H.A. Koistinen, I. Kolcic, C. Kooperberg, J.E. Krieger, S.B. Kritchevsky, M. Kubo, J. Kuusisto, T.A. Lakka, C. D. Langefeld, C. Langenberg, L.J. Launer, B. Lehne, R.N. Lemaitre, Y. Li, J. Liang, J. Liu, K. Liu, M. Loh, T. Louie, R. Mägi, A.W. Manichaikul, C.A. McKenzie, T. Meitinger, A. Metspalu, Y. Milaneschi, L. Milani, K.L. Mohlke, T.H. Mosley, K. J. Mukamal, M.A. Nalls, M. Nauck, C.P. Nelson, N. Sotoodehnia, J.R. O'Connell, N.D. Palmer, R. Pazoki, N.L. Pedersen, A. Peters, P.A. Peyser, O. Polasek, N. Poulter, L.J. Raffel, O.T. Raitakari, A.P. Reiner, T.K. Rice, S.S. Rich, A. Robino, J.G. Robinson, L.M. Rose, I. Rudan, C.O. Schmidt, P.J. Schreiner, W.R. Scott, P. Sever, Y. Shi, S. Sidney, M. Sims, B.H. Smith, J.A. Smith, H. Snieder, J.M. Starr, K. Strauch, N. Tan, K.D. Taylor, Y.Y. Teo, Y.C. Tham, A.G. Uitterlinden, D. Van Heemst, D. Vuckovic, M. Waldenberger, L. Wang, Y. Wang, Z. Wang, W. Bin Wei, C. Williams, G. Wilson, M.K. Wojczynski, J. Yao, B. Yu, C. Yu, J.M. Yuan, W. Zhao, A.B. Zonderman, D.M. Becker, M. Boehnke, D.W. Bowden, J.C. Chambers, I. J. Deary, T. Esko, M. Farrall, P.W. Franks, B.I. Freedman, P. Froguel, P. Gasparini, C. Gieger, B.L. Horta, Y. Kamatani, N. Kato, J.S. Kooner, M. Laakso, K. Leander, T. Lehtimäki, P.K.E. Magnusson, B. Penninx, A.C. Pereira, R. Rauramaa, N. J. Samani, J. Scott, X.O. Shu, P. Van Der Harst, L.E. Wagenknecht, Y.X. Wang, N. J. Wareham, H. Watkins, D.R. Weir, A.R. Wickremasinghe, W. Zheng, P. Elliott, K. E. North, C. Bouchard, M.K. Evans, V. Gudnason, C.T. Liu, Y. Liu, B.M. Psaty, P. M. Ridker, R.M. Van Dam, S.L.R. Kardia, X. Zhu, C.N. Rotimi, D.O. Mook-Kanamori, M. Fornage, T.N. Kelly, E.R. Fox, C. Hayward, C.M. Van Duijn, E.S. Tai, T.Y. Wong, J. Liu, J.I. Rotter, W.J. Gauderman, M.A. Province, P.B. Munroe, K. Rice, D.I. Chasman, L.A. Cupples, D.C. Rao, A.C. Morrison, Multiancestry genome-wide association study of lipid levels incorporating gene-alcohol interactions, Am. J. Epidemiol. 188 (2019) 1033–1054, https://doi.org/10.1093/aje/kwz005.