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**Abstract**

The last few decades have witnessed a global rise in the number of older people. Despite this demographic shift, morbidity within this population group is high. Many factors influence healthspan; however an obesity pandemic is emerging as a significant determinant of older peoples' health. It is well established obesity adversely effects several metabolic systems. However, due to its close association with overall cardiometabolic health, the impact obesity has on cholesterol metabolism needs to be recognised. The aim of this review is to critically discuss the effects obesity has on cholesterol metabolism and to reveal its significance for healthy ageing.

**Keywords:** Ageing, older people, cholesterol metabolism, obesity, oldest old

## 1. Introduction

In 2030 older people (persons aged ≥60 years) are projected to account for almost 20% of the global population[1]. Despite this demographic shift in favour of older people, morbidity among this group is high[2]. Many factors impact older peoples' health; however an obesity pandemic is emerging as a significant global health concern[3; 4; 5; 6; 7]. Microcosmically, the UK illustrates the extent of the global obesity problem. Among females aged 65-74 years in the UK 30% have a body mass index (BMI) ≥30 kg/m$^2$, and are categorised as obese[8]. The problem is even more pronounced among their male counterparts, as 33% of males are categorised as obese within this age group[8]. The problem extends to those aged ≥75 years, as 28% of females are obese, while 23% of males are obese in this age group. From a public health perspective these figures are alarming because obesity adversely effects several metabolic systems, and is synonymous with many conditions including, cancer, type 2 diabetes mellitus (T2DM), hypertension and dyslipidemia[9; 10; 11]. However, due to its close association with overall cardiometabolic health, the impact obesity has on cholesterol metabolism needs to be recognised[12; 13]. The aim of this review is to critically discuss the effects obesity has on cholesterol metabolism and to reveal its significance for healthy ageing.

## 2. An overview of cholesterol metabolism

Figure 1 outlines that cholesterol balance is maintained by the body responding to changes in ingestion, absorption, synthesis and excretion[14]. Humans ingest a modest amount of dietary cholesterol (DC), which mixes with intestinal cholesterol[15]. Absorption is controlled by cholesterol ester hydrolase which liberates cholesterol esters (CE), facilitating the inclusion of free cholesterol (FC) into bile acid micelles[16]. The intestinal protein Niemann-Pick C1-Like 1 (NPC1L1) mediates cholesterol absorption into the enterocyte by clathrin-mediated endocytosis[17]. ATP-binding cassette (ABC) transporters G5 and G8 (ABCG5/G8) control the efflux of cholesterol from the enterocytes to the lumen[18]. Within the enterocyte, acetyl CoA acetyltransferase 2 (ACAT2) re-esterifies cholesterol[19], which is combined with apolipoprotein B-48 (apoB-48), triglycerides (TGs) and phospholipids, to generate a chylomicron[20]. Upon entering the bloodstream, chylomicrons are acted on by lipoprotein lipase (LPL), which catalyses their TGs, liberating free fatty acids (FFAs)[21]. Chylomicron remnants are removed from the circulation by hepatic remnant receptors[22].

The liver is the main site of cholesterol synthesis[23], providing cholesterol and TGs for the assembly of very low density lipoproteins (VLDLs)[24]. In the plasma, LPL hydrolyses VLDLs to low density lipoproteins (LDLs), via intermediate density lipoproteins (IDLs)[25]. LDL-cholesterol (LDL-C) is removed by the LDL receptor (LDLr)[26] and LDLr-related protein 1 (LRP1)[27]. This process is governed by intracellular sterol levels[28]. Increasing intracellular cholesterol activates, insulin-induced genes (Insigs) proteins. Insig-1 and Insig-2 bind to sterol regulatory element-binding protein cleavage-

activating protein (SCAP) in the endoplasmic reticulum (ER), restricting the migration of the SCAP/ sterol regulatory element-binding protein (SREBP) complex to the Golgi[29; 30]. When sterol levels drop, SREBP-2 migrates to the Golgi where it is cleaved by subtilisin kexin isozyme/Site-1 protease (SKI-1/S1P), and the intramembranous metalloprotease Site-2 protease (S2P)[31]. This releases the NH-terminal domain of SREBP-2 from the membrane. Two N-terminal fragments dimerize, then interact with importin-β, before entering the nucleus, to activate SREBP-2-regulated gene promoters[32]. A further regulatory point involves LDLr synthesis. Nuclear SREBP-2 increases the transcription of proprotein convertase subtilisin/kexin type 9 (PCSK9)[33]. PCSK9 reduces the number of LDLrs by increasing their metabolism, and subsequent degradation, restricting LDL uptake[33]. High cellular cholesterol levels suppress SREBP-2 release from the ER, thus PCSK9 transcription is reduced, which subsequently increases LDLRr levels[34]. The synchronised interplay of SREBP-2 induced transcription of both LDLr and PCSK9 regulates circulating LDL-C levels. Additionally, cholesterol entering a hepatic cell as part of LDL triggers ACAT2[26], which catalyses FC to CE[19], and this cholesterol also activates cholesterol 7α - hydroxylase (CYP7A1), the rate-limiting enzyme of bile acid synthesis[35].

By disrupting any of the mechanisms I have discussed, obesity has the potential to provoke a rise in plasma LDL-C. Elevated LDL-C levels are inexorably linked to an increased risk of atherosclerotic-cardiovascular disease (CVD)[36; 37; 38]. Moreover, emerging evidence suggests suboptimal LDL-C levels, in tandem with elevated serum uric acid, could present an increased risk of developing hypertension or metabolic syndrome[39; 40].

A further important aspect of cholesterol metabolism is reverse cholesterol transport (RCT). RCT removes excess cholesterol from peripheral tissue[41]. High density lipoproteins (HDLs) are central to this. HDLs “mop up” excess cholesterol, generating HDL-cholesterol (HDL-C)[42]. Central to RCT is the ferrying of FC and phospholipids to lipid-free apo A-I to form nascent pre-β HDL particles, in a process primarily regulated by ABCA1[43; 44]. Nascent HDLs progress to mature HDLs due to the esterification of cholesterol by lecithin-cholesterol acyltransferase (LCAT)[45]. Cholesterol within HDLs can follow one of two routes to the liver. HDLs can go directly to the liver and deposit their cholesterol by interacting with scavenger receptor class B, type 1 (SR-B1) receptors[46]. Secondly, cholesterol can be transferred to the liver via the action of cholesteryl ester transfer protein (CETP), which redistributes cholesterol to LDL and VLDL[47]. Regardless of the route, HDLs transfer cholesterol to the liver, where it can be effluxed directly as cholesterol or converted to bile salts[48]. It can then be excreted during enterohepatic circulation. Consequently, RCT is regarded as antiatherogenic[49];this is underscored by studies which have revealed an inverse relationship between HDL-C levels and the onset of premature CVD[50; 51]. Intriguingly, HDL’s antiatherogenic role is thought to be enhanced further by possessing antioxidant properties[52]. As with the mechanisms which regulate LDL-C levels,

if obesity interferes with the processes underpinning RCT, this has the potential to modulate an individual's risk of CVD.

## 3. Obesity and cholesterol metabolism

### *3.1 Cholesterol absorption*

In pioneering work, Miettinen and Kesäniemi (1989) identified a negative correlation between the fractional absorption of DC and obesity in middle aged men; although, a mechanistic explanation for this result was not immediately apparent[53]. In a follow up investigation cholesterol absorption was also found to be inhibited in obese middle aged males (BMI >31 kg/m$^2$)[54]. On this occasion two explanations were proposed for this finding. It was posited labelled DC could have contributed to sub-normal cholesterol absorption. Secondly, it was suggested that cholesterol absorption was inhibited by expanded biliary secretion. However, the precise reason why obesity inhibited cholesterol absorption remained unclear. More recent studies have added further intrigue to this puzzle. It has been found that treatment of obese hypercholesterolemic subjects with the NPC1L1 inhibitor, Ezetimibe, improved the lipid profile and insulin resistance (IR) in these subjects[55; 56]. This suggests obesity could in fact increase cholesterol absorption in obese subjects rather than inhibiting it, and an arbiter of this change could be NPC1L1. If obesity does increase cholesterol absorption, this effect could also be induced by provoking a rise in circulating bile acids. For example, Vincent et at. (2013) found that the post-prandial bile acid response is increased in obese male and female patients with T2DM compared to age-matched normoglycaemic individuals[57]. Further evidence that obesity influences bile acid metabolism comes from studies of the gut microbiome[58]. For instance, in one study it was found that bile salt hydrolase (BSH) is the arbiter of host-microbiome interactions which modulated weight gain, and lipid metabolism in a murine model[59]. Specifically, the expression of cloned BSH enzymes in the gastrointestinal tract of gnotobiotic or conventionally raised mice significantly modified plasma bile acid signatures and regulated the transcription of important genes involved in cholesterol metabolism (Abcg5/8) both hepatically and intestinally. Moreover, high-level expression of BSH in conventionally raised mice resulted in a significant drop in host weight gain, plasma cholesterol levels, and hepatic TGs. As an adjunct to this finding it has been shown that the farnesoid X receptor (FXR) has a central role to play in modulating host-microbiome dialogue. For instance, mouse models of diet-induced obesity have shown that both the microbiome and FXR signalling are required for weight gain[60; 61].

*3.2 Cholesterol synthesis*

Cholesterol synthesis is also affected by obesity; sterol-balance studies have shown increased weight gain results in a higher rate of cholesterol synthesis[62; 63]. It is uncertain how weight gain induces a higher rate of cholesterol synthesis. However, it is important to acknowledge that hepatic HMGCR increases in obese subjects[64]. This would naturally result in an increase in hepatic cholesterol production; something which has been observed in obese subjects[65]. For example, in a study involving 17 morbidly obese middle-aged males, it was found that the activity, and mRNA levels of HMGCR, was higher in the obese subjects, when compared to lean control group[66]. Moreover, the activity and mRNA level of cholesterol 7 alpha-hydroxylase, also increased compared to controls. The activity of ACAT2, and LDLr mRNA levels were elevated in these subjects. Such alterations have the potential to impact the normal functioning of hepatic LDLr. For example, it was also found in this study that the binding of LDL to the LDLr was reduced by fifty percent when compared with controls[66].

*3.3 Hepatic free cholesterol/ bile acid accumulation and Non-alcoholic fatty liver disease*

Non-alcoholic fatty liver disease (NAFLD) encompasses a number of hepatic pathologies, from fatty liver disease to non-alcoholic steatohepatitis (NASH); a condition which can progress to cirrhosis[67; 68; 69; 70; 71]. NAFLD has a higher occurrence in males than females, and its prevalence increases with age[72; 73]. NAFLD is closely associated with IR and hyperinsulinemia and is prevalent in 70-80% of obese individuals[74]. Moreover, it has recently been associated with key parameters of cardiovascular health, including arterial stiffness[75]. Traditionally, NAFLD has been associated with increased hepatic TGs, however in recent years there has been growing evidence linking altered cholesterol metabolism with the aetiology of NAFLD[76; 77; 78]. For instance, hepatic FC accumulates in obese diabetic mice and results in steatohepatitis[79]. Most recently in mice it has been found that found that hepatic cholesterol, but not hepatic TG, increased with age[80]. Focusing on humans the intake of high levels of DC have been associated with NASH[81; 82]. Mechanistically, it would appear cholesterol synthesis is upregulated in NAFLD. This was demonstrated by a study which examined the expression of an array of genes associated with cholesterol metabolism[83]. In the investigation, 20 middle aged subjects with NAFLD (mean BMI 34.1 kg/m$^2$) and NASH (mean BMI 34.2 kg/m$^2$) were compared to 20 obese controls (33.2 kg/m$^2$) and 6 lean normal controls (mean BMI 21.4 kg/m$^2$). It was found NAFLD was associated with increased SREBP-2 maturation, HMGCR expression and decreased phosphorylation of HMGCR. Additionally, cholesterol ester hydrolase was increased, while ACAT2 remained unchanged. Moreover, LDLr expression decreased significantly. Also, HMGCR expression was correlated with FC, histologic severity of NAFLD and LDL-C levels. Bile acid homeostasis is also affected as a result of NAFLD[84]. Individuals with NASH have elevated levels of bile acids which can accumulate hepatically[85]. Bile acid signalling is regulated by the Farnesoid X receptor (FXR), which contributes to overall cholesterol metabolism [84]. Interestingly, it has been shown in mice that the gut microbiota can modulate obesity via this receptor. The gut microbiota promoted weight gain and hepatic steatosis in an FXR-dependent

manner between Fxr-/- and wild-type mice [60]. Moreover, bile acid profiles and the composition of faecal microbiota differed between Fxr-/- and wild-type mice. The finding that the gut microbiota induced liver steatosis in an FXR-dependent manner was suggested to be induced by the increased expression of CD36, Apolipoprotein C2, and VLDL receptor, all of which are involved in lipoprotein uptake. Thus, increased steatosis was thought to be attributed to the augmented expression of lipogenic genes or diminished expression of genes associated with fatty acid oxidation. In terms of promoting obesity mechanistically the authors showed that the gut microbiota of Fxr-deficient mice was defined by a phylum-wide rise in Bacteroidetes and phylum-wide reduction of Firmicutes. Thus, the gut microbiota changes in response to diet and is associated with an obesity phenotype, which is mediated by FXR signalling.

*3.4 Lipoprotein dynamics and RCT*

Lipoprotein processing is significantly impaired due to obesity. Morbidly obese middle aged patients have been found to have lower expression of LPL and LRP1 in their visceral tissue[86]. LPL expression was also lower in the subcutaneous adipose tissue of these subjects. The decrease in the expression of LRP1 is likely a contributing factor to the increase in plasma LDL-C, which often, but not always, accompanies obesity[87]. More strikingly, obesity has regularly been associated with an increase in atherogenic small dense LDL[88; 89; 90]. Obesity also lowers HDL-C regardless of age, sex or ethnic background, while an inverse association between HDL-C levels and BMI has also been observed[91; 92; 93]. Intriguingly, in the Framingham offspring study, the effect of increased BMI on total cholesterol and LDL-C was not as strong as it was for HDL-C[94]. More recently, an inverse association has been found between LDL-C and BMI in morbidly obese subjects[95]. Low levels of the major apolipoprotein component of HDL (Apo A-I) have also been found to be associated with obesity in the Framingham Offspring Study in men and women[96]. Moreover, it has been revealed in a mouse model that increased Apo A-I could have an anti-obesity effect. Increased energy expenditure and up-regulation of uncoupling protein 1 in brown fat were associated with high levels of Apo A-I[97]. In addition, other apolipoproteins have been shown to be influenced by obesity. Elevated levels of fasting and postprandial apo B-48 have been measured in obese human subjects[66]. Obesity could also impact the functional capacity of HDL-C. For example, the antioxidant capacity of HDL appears to be compromised in obese subjects[98]. Obesity interferes with other components of RCT, for example, obesity causes impairment in RCT due to reduced plasma cholesterol uptake and efflux by hepatocytes and adipocytes in *ob/ob* mice[99]. Plasma CETP levels have also been positively correlated with obesity[100]. The likely reason for this finding, is that adipose tissue is a significant source of CETP[101]. Intriguingly, LCAT deficiency has been suggested to confer a degree of protection from the development of obesity. Tentative evidence for this finding comes from a study of LCAT null mice which appeared to be protected from diet-induced obesity[102].

## 4. Commonality between obesity and ageing

It is possible obesity superimposed on ageing could expedite the age associated dysregulation of cholesterol metabolism[103; 104; 105]. Taking LDL-C as an example, increasing age is associated with a rise in LDL-C in males and females, in both cross-sectional[106; 107] and prospective studies[108; 109]. It is not known how ageing contributes to a rise in LDL-C; however, there are solid reasons to believe a decline in the hepatic clearance rate of LDL-C is a factor[110; 111]. For example, human ageing is associated with a drop in the number of hepatic LDLr[112]. Obesity can also results in a rise in LDL-C[113; 114], although in some observational studies it is only weakly associated[115; 116],or not associated at all[117]. An obesity induced rise in LDL-C could have the same mechanistic underpinning as ageing, because it is also associated with a decline in hepatic LDLr numbers. Also similar to obesity, HDL-C levels decrease with age in humans in certain studies[118]. For instance, HDL-C levels have been observed to decrease with age in both men and women in prospective studies[109; 119]. Although HDL-C levels do not change with age in most cross-sectional studies[120; 121], they have been shown to decrease in others[122]. A decline in HDL-C with age could be due to disrupted CETP activity. If this is the case it would be mechanistically similar to the putative effect obesity has on RCT[100]. Ageing also impacts lipoprotein processing by reducing the activity of plasma LPL by as much as 55-60%[123; 124]. This is similar to the metabolic affect obesity has on LPL[125]. In rodents it has been found that bile acid synthesis diminishes with age[126]. This is also similar to obesity because in men and women a decrease in the conversion of cholesterol to bile acids has been identified in certain studies[127; 128]. However, other studies conflict with this and suggest obesity results in an increase in bile acid synthesis[129].

The landscape of an obese state also resonates with the free radical theory of ageing[130]. For example, obesity is associated with oxidative stress via increased generation of reactive oxygen species (ROS)[131]. As visceral fat stores increase, adipocytes generate increasing levels of ROS [132]. Consequently, oxidative stress results in IR within adipose and peripheral tissue[133]. It has been suggested that high levels of ROS impinge on intracellular cholesterol homeostasis[134]. ROS have been found to upregulate the activity of hepatic HMGCR in rodent hepatic tissue, leading to an increase in cholesterol synthesis[80; 135; 136; 137] ROS are also implicated in the pathogenesis of atherosclerosis, where oxidation of LDL is regarded as a key event in the initial stages of atherosclerosis formation[138]. Despite the many parallels between obesity and ageing a number of difference do exist. In contrast to obesity it has been revealed that cholesterol absorption efficiently increases with age, however there is a paucity of evidence for this in humans and findings are confined to rodent studies[139]. Mechanistically it appears ageing suppresses the expression of *Abcg5* and *Abcg8*, and upregulates the expression of *Npc1l1* in murine models[140]. In rodents it has been found that bile acid synthesis declines with age[126]. This contrasts with obesity. Also, unlike obesity, it has been found that hepatic ACAT2 activity decreases with age in Watanabe heritable hyperlipidemic rabbits[141].

## 5. Diet: A key modulator of obesity and cholesterol metabolism

An obese state is the result of an imbalance between the amount of calories consumed by an individual and the amount of energy they expend[142]. Moreover, it is generally regarded that excess consumption of dietary fat plays a role in the development of obesity[143]. Taking this a step further, a clear link between diet, cholesterol metabolism and obesity centres on the excessive intake of DC. For instance, DC has been shown to exacerbate hepatic steatosis and inflammation in obese LDLr-deficient mice[144]. Moreover, in this study, the consumption of DC exacerbated hepatic macrophage infiltration, apoptosis, and oxidative stress. Excessive intake of DC has also been shown to result in the accumulation of hepatic cholesterol in obese diabetic mice[79]. The accumulation of cholesterol was attributed to changes in some of the regulator mechanisms discussed previously, including the up-regulation of LDLr, via activation of SREBP-2, a drop in the conversion of cholesterol to bile acids, and suppression of bile acid excretion in bile.

In addition to the intake of fat/DC, high intakes of dietary sugars have been associated with obesity and unfavourable lipid levels in both men and women[127; 128]. In particular dietary fructose has emerged as an important dietary factor which contributes to the hepatic dysregulation of cholesterol metabolism [69; 145]. For instance, high fructose consumption increases serum PCSK9 concentrations and reduces liver LDLr protein levels in hyperlipidemic hamsters[146]. In humans, it has been found that the consumption of fructose and high fructose corn syrup increases LDL-C, and apo-B in both men and women[147]. Moreover, NASH is associated with animal models fed a high fat, high fructose diet[148; 149]. Consumption of excessive dietary fructose has also been associated with cognitive decline in older adults[150]. This is intriguing because obesity can be correlated with poor cognitive performance in older adults[151]. Taking this a step further, it is possible fructose makes a mechanistic contribution to the pathogenesis of Alzheimer's disease by interfering with lipid metabolism. For example, animal models of dementia suggest excessive consumption of fructose induce IR and promote dementia pathogenesis[152; 153; 154]. This is thought to occur as follows, IR is associated with elevated plasma ceramides which interfere with lipoprotein metabolism and amyloidogenic processing resulting in the deposition of β-amyloid peptides, which is a hallmark of Alzheimer's disease[155].

In certain circumstances age could potentially offer a degree of protection against diet-induced obesity. In a recent study which compared the response of young and old mice to a Western diet (WD), it was found that old mice did not show a higher body weight or adipose tissue mass, when compared to their young counterparts[156]. Significantly, and of direct relevance to the underlying hepatic health of older people, it was found that the aged mice did have a build-up of hepatic lipid on the WD. As well as the type and amounts of nutrients consumed, it has been found that meal frequency, timing, and regularity are also associated with obesity[157]. Recently this has been shown to have important implications for cholesterol metabolism. In a cross-sectional study of non-institutionalized and non-pregnant healthy

Taiwanese adults (≥19-years-old) found that higher energy intake at night time is associated with elevated total and LDL-C levels[158]. This was an interesting finding, although a mechanistic explanation for this discovery was not posited. Regardless, the study presents the possibility that meal timing and frequency could impact both obesity and cholesterol metabolism which is an intriguing prospect.

Alcohol consumption also effects cholesterol metabolism. Evidence suggests moderate to low alcohol consumption increases levels of HDL-C and decreases levels of LDL-C [159]. However, it is important to be cautious as alcohol has a limited therapeutic range and only modest drinking appears to be beneficial. This is partly due to the caloric richness of alcohol, as its excessive consumption can result in increased weight gain in certain individuals[160]. Moreover, chronic alcohol intake affects lipid metabolism broadly by provoking the increased synthesis of TGs and subsequent hypertriglyceridemia[161]. In addition, it has been observed that alcohol consumption decreases the activity of LPL, which is also associated with hypertriglyceridemia[162]. From the perspective of HDL metabolism, in individuals with alcohol dependence syndrome no association between plasma-HDL-C and the number of drinks consumed per day has been observed in these individuals, indicating that only low level consumption of alcohol is beneficial[163]. Furthermore, in a longitudinal study of alcohol consumption, the long-term effect of total alcohol consumption on the change in HDL-C was observed to be a nonlinear relationship[164]. The mechanistic explanation for this is thought to centre on the pathophysiological effect of alcohol on the liver which results in a decrease in the hepatic production of HDL in these subjects[165].

Alarmingly, the excessive intake of alcohol has been increasing among older people in certain populations[166]. In a recent study involving a cohort of Australian males (≥ 65 years), which explored the association between alcohol intake and body composition, it was found that participants who consumed ≥5 alcoholic drinks/day had a greater BMI, fat mass index, waist circumference, percent body fat and lower lean mass than non-drinkers[167]. This has metabolic consequences for older people because alcohol consumption augments lipid synthesis via sterol SREBP-1[168]. This is possibly mediated by acetaldehyde, which contributes to an increase in the synthesis of SREBP-1, which in turn augments cholesterol and fat synthesis[168]. Alcohol consumption has also been shown to dysregulate hepatic fatty acid oxidation[169] and decrease the secretion of VLDL[170]. A drop in VLDL secretion could result in a decrease in the conversion of VLDL-C to LDL-C, and be responsible for the decrease in LDL-C associated with low to moderate alcohol intake[171]. Furthermore, this mechanism could explain the decreased risk of alcohol dependence with increased LDL-C levels identified among some of the participants of a recent case control study investigating alcohol consumption and obesity[172].

On the flip side of the coin, emerging research has revealed that certain novel dietary components improve both cholesterol metabolism and have anti-obesity effects. For example, a diet high in fruit and

vegetables is associated with a lower risk of obesity/body adiposity[173; 174; 175]. Moreover, certain components of fruits and vegetables have a favourable effect on cholesterol metabolism. For instance, soluble fibre exerts a favourable effect by decreasing LDL-C levels[176]. It has been found that 3g per day of soluble fibre can lower total and LDL-C by ~0.13 mmol/L[177]. Several mechanisms have been suggested to account for this effect, including the inhibition of bile salt intestinal re-absorption, and a diminished glycemic response, which results in a drop in insulin stimulated hepatic cholesterol synthesis[178]. The gut is also thought to be the site of action of plant sterols. Plant sterols are naturally occurring compounds found in fruit and vegetables which are structurally related to cholesterol differing only in the structure of their side chains[179]. Consumption of 1.8-2.0 g/day of plant sterols has been shown to lower both total and LDL-C concentrations by 10%-15% in different population groups[180; 181]. Although the precise mechanism by which LDL-C is lowered is uncertain, it is generally regarded that plant sterols inhibit intestinal cholesterol absorption[182]. Not only have plant sterols been associated with decreased LDL-C. More recently, the consumption of high levels of phytosterols, which includes plants sterols, have been associated with decreased rates of obesity. For example, a recent cross-sectional study of Chinese adults (18-60 years) revealed that higher consumption of phytosterols was associated with lower BMI, waist circumference, and a lower prevalence of overweight/obesity/abdominal obesity in this population group[183]. Intriguingly the administration of both phytosterols and red rice were recently studied in mildly hypercholesterolemic subjects[184]. In tandem these two nutraceuticals had a more significant impact on LDL-C levels, when compared to either phytosterols or red rice on their own. Diet also has an important role to play in terms of alleviating the metabolic consequence of obesity. Most recently, it has been shown that medium chain saturated fatty acids (MCSFA) could illicit a degree of protection against obesity-induced comorbidities such as diabetes in obesogenic mice[185]. Moreover, in a rat model it has been found that MCSFA could help prevent NAFLD[186]. Mechanistically, it is thought the beneficial effects of MCSFA consumption could be induced via their preferential β-oxidation over long chain saturated fatty acids[187]. A further way diet has been suggested to provide a means of treating obesity is by modulating the gut microbiome. For instance, in an obese population which adhered to a Mediterranean diet (MD) for a year, it was found that the MD exerted a protective effect against T2DM development by modulating specific changes in the gut microbiota. Specifically, this involved increasing the abundance of *Faecalibacterium prausnitzii* and *Roseburia* species.

## 6. Cholesterol metabolism and obesity in older people

Certain individuals have a metabolic profile which does not appear to be overtly affected by obesity. Such individuals are known as “metabolically healthy obese" (MHO)[188]. In a study which investigated obesity in the US population, it was found 31.7% of obese adults (~19.5 million), were MHO[189]. The prevalence of metabolically healthy older individuals was 14.3% among those aged 65-79 years, and

22.1% among those ≥80 years. Healthy participants were defined by having 0 or 1 cardiometabolic abnormality. Unhealthy individuals were defined as having ≥2 cardiometabolic abnormalities. Among individuals with ≥2 metabolic abnormalities, the two most common cardiometabolic risk factor combinations, were high TG level/low HDL-C level and high blood pressure/high glucose level. In a similar investigation it was found that among participants with ⩽1 metabolic abnormality, obesity was associated with a greater risk of developing multiple metabolic abnormalities[190]. Significantly, lipid metabolism was also key, as TG and HDL-C levels predicted an individual's progression to a metabolically unhealthy obese (MUHO) state. Within obesity research, a further puzzle exists; there are situations where being overweight/mildly obese appears to be beneficial. This is known as the "obesity paradox"[191]. In an ageing context, the obesity paradox appears to confer a survival advantage in older patients (generally those >50 years) who have conditions such as, CVD, arthritis and kidney disease[192]. Focusing specifically on cholesterol metabolism, and its intersection with the obesity paradox, normal total serum cholesterol levels have been reported in morbidly obese individuals. In a study of 3,312 women (≥ 18 years) it was found the percentage of individuals with normal total serum cholesterol levels (<200 mg/dL) decreased with increasing BMI, from 55% in those with a BMI <20 kg/m$^2$ to 28% in women with a BMI of 30-35 kg/m$^2$[193]. Total serum cholesterol >7.75 mmol/l was found in 2% of individuals with a BMI <20 kg/m$^2$, but in 6% of the group with a BMI between 30 and 35 kg/m$^2$. Among morbidly obese women (BMI >40 kg/m$^2$), 39% had total serum cholesterol levels <5 mmol/l. Thus, it would appear in morbidly obese women, there is a significant number of individuals with normal total serum cholesterol levels. Such findings were also identified in a study which examined individuals (20–64 years) with a BMI in the range 34-77 kg/m$^2$[194]. It was found that mean total cholesterol levels in the obese group fell with increasing BMI. Moreover, LDL-C levels were lower in obese men (3.65 mmol/l versus the control group, 4.17 mmol/l).

The association between obesity and cholesterol metabolism has been studied to a limited extent in the oldest old (individuals ≥80 years). Despite this, the oldest old who are obese have a higher prevalence of morbidity[195]. In a study which examined the oldest old among a group aged 60-85 years, it was reported that obesity was associated with shorter survival plus a higher incidence of coronary heart disease and T2DM[196]. When cholesterol metabolism has been examined in the oldest old some intriguing findings have been revealed. In the Leiden 85-Plus Study it was observed that both high and low levels of LDL-C had a similar impact on mortality risk[197]. Interestingly, this finding occurred despite CVD being the main cause of mortality in these subjects. Similar observations have been identified in several other studies which have examined the lipoprotein profile of the oldest old[198; 199]. Interestingly, during a three year follow up study involving the Chinese oldest old it was found that for each 1 mmol/L increase of LDL-C concentration there was a corresponding 19% decrease in 3-year all-cause mortality [200]. These findings are intriguing and require a biological explanation. The oldest old in general are in a state of multi-morbidity[201]. Based on this premise it is logical that low levels of

LDL-C could be one particular clinical manifestation of underlying multi-morbidity. Ageing superimposed on cholesterol metabolism in a MUHO individual or a metabolically unhealthy normal weight individual could theoretically contribute to a drop in LDL-C. The conceptual framework outlined in figure 2 suggests an obese state/poor metabolic health combined with an age associated rise in hepatic ROS levels results in a rise in HMGCR activity[202; 203]. In a normolipidemic individual this would result in rise in LDL-C due to the homeostatic down-regulation of LDLr synthesis. However, if there is also an age associated decrease in ACAT2 activity, this reduces the conversion of FC to CE. Consequently, VLDL-C production would drop and there would be a concomitant reduction in LDL-C. As intracellular levels of FC accumulate and oxidative stress progresses, this state could advance to NAFLD[204]. As there is a strong association between NAFLD[205] and CVD[206], this in theory could increase an older persons risk of mortality, and help to account for the association between low levels of LDL-C and increased risk of mortality, which has been observed in certain studies involving the oldest old.

## 7. Conclusions

Obesity among older people has increased significantly. This review has revealed that obesity has a pleiotropic effect on cholesterol metabolism. Obesity affects cholesterol absorption, synthesis, lipoprotein processing, and results in the accumulation of cholesterol hepatically. Many of the changes are similar to how ageing intersects with cholesterol metabolism, and it can be suggested an obese state superimposed on ageing has the potential to exacerbate the dysregulation of cholesterol metabolism, which occurs with advancing age. This review also revealed diet as a key factor which links an obese state to important changes which occur in hepatic cholesterol metabolism. In particular the excessive intake of dietary lipids and fructose were highlighted as key factors which underpin conditions such as NAFLD. Careful attention needs to be placed on this association. This review also highlighted a number of anomalies which exist in this field. Firstly, there are certain individuals who, despite being in an obese state, appear to be normolipidemic, and it is not immediately clear why this is the case. The second anomaly centres on the oldest old. In particular the association between low levels of LDL-C and an increased risk of mortality, which has been observed in a number of studies. A tentative explanation for this association was presented, which centred on obesity/an unhealthy metabolic state and its intersection with ageing as important factors underpinning this anomaly. However, this is only one possible explanation and to fully elucidate this intriguing anomaly, it is necessary for the dynamics of cholesterol metabolism in the oldest old to be investigated to a much greater extent. To date there has been paucity of research in this area. Finally, this review has raised a broader question which relates to the public health challenge surrounding an ageing global population which is becoming increasingly obese. There is no straightforward solution to this problem. However, one possible strategy could involve adopting public health initiatives which target middle aged individuals and educating them about the deleterious health implications of being overweight/obese. Increased awareness among this

group could lead to better health in later life. To this end it is vital public health interventions are initiated which make both younger people and middle-aged individuals cognisant of appropriate lifestyle choices which optimise their chances of growing old healthily. If this issue is not addressed in coming years, more and more people will reach old age in poor metabolic heath due to being obese.

## References


1. United Nations (2017) Department of Economic and Social Affairs, Population Division (2017). World Population Ageing 2017 - Highlights (ST/ESA/SER.A/397).
2. Kingston A, Robinson L, Booth H *et al.* (2018) Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. *Age Ageing* **47**, 374-380.
3. Starr KNP, Bales CW (2015) Excessive body weight in older adults. *Clinics in geriatric medicine* **31**, 311-326.
4. Jura M, Kozak LP (2016) Obesity and related consequences to ageing. *Age (Dordrecht, Netherlands)* **38**, 23-23.
5. Kalish VB (2016) Obesity in older adults. *Primary Care: Clinics in Office Practice* **43**, 137-144.
6. Afshin A, Forouzanfar MH, Reitsma MB *et al.* (2017) Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* **377**, 13-27.
7. Morgan A, Mooney K, Mc Auley M (2016) Obesity and the dysregulation of fatty acid metabolism: implications for healthy aging. *Expert Rev Endocrinol Metab* **11**, 501-510.
8. Baker C (2018) Obesity Statistics, House of commons Briefings Paper, Number 3336,20 March 2018.
9. Pi-Sunyer X (2009) The medical risks of obesity. *Postgrad Med* **121**, 21-33.
10. Bell SP, Saraf AA (2016) Epidemiology of Multimorbidity in Older Adults with Cardiovascular Disease. *Clin Geriatr Med* **32**, 215-226.
11. Reilly JJ, Methven E, McDowell ZC *et al.* (2003) Health consequences of obesity. *Arch Dis Child* **88**, 748-752.
12. Mc Auley MT (2019) Aging and Cholesterol Metabolism. In *Encyclopedia of Gerontology and Population Aging*, pp. 1-6 [D Gu and ME Dupre, editors]. Cham: Springer International Publishing.
13. Mc Auley MT, Mooney KM (2014) Lipid metabolism and hormonal interactions: impact on cardiovascular disease and healthy aging. *Expert Review of Endocrinology & Metabolism* **9**, 357-367.
14. van der Wulp MY, Verkade HJ, Groen AK (2013) Regulation of cholesterol homeostasis. *Mol Cell Endocrinol* **368**, 1-16.
15. Lu K, Lee MH, Patel SB (2001) Dietary cholesterol absorption; more than just bile. *Trends Endocrinol Metab* **12**, 314-320.
16. Shamir R, Johnson WJ, Zolfaghari R *et al.* (1995) Role of bile salt-dependent cholesteryl ester hydrolase in the uptake of micellar cholesterol by intestinal cells. *Biochemistry* **34**, 6351-6358.
17. Jia L, Betters JL, Yu L (2011) Niemann-pick C1-like 1 (NPC1L1) protein in intestinal and hepatic cholesterol transport. *Annu Rev Physiol* **73**, 239-259.
18. Li G, Gu HM, Zhang DW (2013) ATP-binding cassette transporters and cholesterol translocation. *IUBMB life*.
19. Chang TY, Li BL, Chang CC *et al.* (2009) Acyl-coenzyme A:cholesterol acyltransferases. *Am J Physiol Endocrinol Metab* **297**, E1-9.
20. Redgrave TG (2004) Chylomicron metabolism. *Biochem Soc Trans* **32**, 79-82.
21. Mead JR, Irvine SA, Ramji DP (2002) Lipoprotein lipase: structure, function, regulation, and role in disease. *J Mol Med (Berl)* **80**, 753-769.

480 22. Cooper AD (1997) Hepatic uptake of chylomicron remnants. *Journal of lipid research* **38**, 2173-
481 2192.
482 23. DeBose-Boyd RA (2008) Feedback regulation of cholesterol synthesis: sterol-accelerated
483 ubiquitination and degradation of HMG CoA reductase. *Cell Res* **18**, 609-621.
484 24. Shelness GS, Sellers JA (2001) Very-low-density lipoprotein assembly and secretion. *Current*
485 *opinion in lipidology* **12**, 151-157.
486 25. Mendivil CO, Zheng C, Furtado J *et al.* (2010) Metabolism of very-low-density lipoprotein and
487 low-density lipoprotein containing apolipoprotein C-III and not other small apolipoproteins.
488 *Arterioscler Thromb Vasc Biol* **30**, 239-245.
489 26. Goldstein JL, Brown MS (2009) The LDL receptor. *Arteriosclerosis, thrombosis, and vascular*
490 *biology* **29**, 431-438.
491 27. van de Sluis B, Wijers M, Herz J (2017) News on the molecular regulation and function of hepatic
492 low-density lipoprotein receptor and LDLR-related protein 1. *Curr Opin Lipidol* **28**, 241-247.
493 28. Brown MS, Goldstein JL (1986) A receptor-mediated pathway for cholesterol homeostasis.
494 *Science* **232**, 34-47.
495 29. Yabe D, Brown MS, Goldstein JL (2002) Insig-2, a second endoplasmic reticulum protein that
496 binds SCAP and blocks export of sterol regulatory element-binding proteins. *Proceedings of the*
497 *National Academy of Sciences* **99**, 12753-12758.
498 30. Yang T, Espenshade PJ, Wright ME *et al.* (2002) Crucial step in cholesterol homeostasis: sterols
499 promote binding of SCAP to INSIG-1, a membrane protein that facilitates retention of SREBPs in ER.
500 *Cell* **110**, 489-500.
501 31. Brown MS, Goldstein JL (1999) A proteolytic pathway that controls the cholesterol content of
502 membranes, cells, and blood. *Proceedings of the National Academy of Sciences of the United States*
503 *of America* **96**, 11041-11048.
504 32. Nagoshi E, Yoneda Y (2001) Dimerization of sterol regulatory element-binding protein 2 via the
505 helix-loop-helix-leucine zipper domain is a prerequisite for its nuclear localization mediated by
506 importin beta. *Mol Cell Biol* **21**, 2779-2789.
507 33. Seidah NG, Awan Z, Chretien M *et al.* (2014) PCSK9: a key modulator of cardiovascular health.
508 *Circ Res* **114**, 1022-1036.
509 34. Lambert G, Charlton F, Rye KA *et al.* (2009) Molecular basis of PCSK9 function. *Atherosclerosis*
510 **203**, 1-7.
511 35. Jackson SM, Ericsson J, Edwards PA (1997) Signaling molecules derived from the cholesterol
512 biosynthetic pathway. *Subcell Biochem* **28**, 1-21.
513 36. Sharrett AR, Ballantyne C, Coady S *et al.* (2001) Coronary heart disease prediction from
514 lipoprotein cholesterol levels, triglycerides, lipoprotein (a), apolipoproteins AI and B, and HDL
515 density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* **104**, 1108-
516 1113.
517 37. Castelli WP, Anderson K, Wilson PW *et al.* (1992) Lipids and risk of coronary heart disease. The
518 Framingham Study. *Ann Epidemiol* **2**, 23-28.
519 38. Boekholdt SM, Arsenault BJ, Mora S *et al.* (2012) Association of LDL cholesterol, non-HDL
520 cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated
521 with statins: a meta-analysis. *Jama* **307**, 1302-1309.
522 39. Cicero AFG, Fogacci F, Giovannini M *et al.* (2019) Interaction between low-density lipoprotein-
523 cholesterolaemia, serum uric level and incident hypertension: data from the Brisighella Heart Study.
524 *J Hypertens* **37**, 728-731.
525 40. Cicero AFG, Fogacci F (2018) Serum uric acid predicts incident metabolic syndrome in the elderly
526 in an analysis of the Brisighella Heart Study. **8**, 11529.
527 41. Favari E, Chroni A, Tietge UJ *et al.* (2015) Cholesterol efflux and reverse cholesterol transport.
528 *Handb Exp Pharmacol* **224**, 181-206.
529 42. Tuteja S, Rader DJ (2014) High-density lipoproteins in the prevention of cardiovascular disease:
530 changing the paradigm. *Clin Pharmacol Ther* **96**, 48-56.

43. Oram JF, Lawn RM (2001) ABCA1: the gatekeeper for eliminating excess tissue cholesterol. *Journal of lipid research* **42**, 1173-1179.
44. Wang S, Smith JD (2014) ABCA1 and nascent HDL biogenesis. *Biofactors* **40**, 547-554.
45. Saeedi R, Li M, Frohlich J (2015) A review on lecithin:cholesterol acyltransferase deficiency. *Clin Biochem* **48**, 472-475.
46. Zhang Y, Da Silva JR, Reilly M *et al.* (2005) Hepatic expression of scavenger receptor class B type I (SR-BI) is a positive regulator of macrophage reverse cholesterol transport in vivo. *Journal of Clinical Investigation* **115**, 2870.
47. Fielding CJ, Fielding P (1995) Molecular physiology of reverse cholesterol transport. *Journal of lipid research* **36**, 211-228.
48. Groen A, Oude Elferink R, Verkade H *et al.* (2004) The ins and outs of reverse cholesterol transport. *Annals of medicine* **36**, 135-145.
49. Rye KA, Bursill CA, Lambert G *et al.* (2009) The metabolism and anti-atherogenic properties of HDL. *Journal of lipid research* **50 Suppl**, S195-200.
50. Castelli WP, Garrison RJ, Wilson PW *et al.* (1986) Incidence of coronary heart disease and lipoprotein cholesterol levels: the Framingham Study. *Jama* **256**, 2835-2838.
51. Abbott RD, Wilson PW, Kannel WB *et al.* (1988) High density lipoprotein cholesterol, total cholesterol screening, and myocardial infarction. The Framingham Study. *Arteriosclerosis, Thrombosis, and Vascular Biology* **8**, 207-211.
52. Soran H, Schofield JD, Durrington PN (2015) Antioxidant properties of HDL. *Front Pharmacol* **6**, 222.
53. Miettinen TA, Kesaniemi YA (1989) Cholesterol absorption: regulation of cholesterol synthesis and elimination and within-population variations of serum cholesterol levels. *The American journal of clinical nutrition* **49**, 629-635.
54. Miettinen TA, Gylling H (2000) Cholesterol absorption efficiency and sterol metabolism in obesity. *Atherosclerosis* **153**, 241-248.
55. Adachi H, Nakano H, Yamamoto K *et al.* (2015) Ezetimibe ameliorates atherogenic lipids profiles, insulin resistance and hepatocyte growth factor in obese patients with hypercholesterolemia. *Lipids in health and disease* **14**, 1.
56. Nakamura A, Sato K, Kanazawa M *et al.* (2018) Impact of decreased insulin resistance by ezetimibe on postprandial lipid profiles and endothelial functions in obese, non-diabetic-metabolic syndrome patients with coronary artery disease. *Heart Vessels*.
57. Vincent RP, Omar S, Ghozlan S *et al.* (2013) Higher circulating bile acid concentrations in obese patients with type 2 diabetes. *Annals of clinical biochemistry* **50**, 360-364.
58. Foley MH, O'Flaherty S, Barrangou R *et al.* (2019) Bile salt hydrolases: Gatekeepers of bile acid metabolism and host-microbiome crosstalk in the gastrointestinal tract. *PLoS pathogens* **15**, e1007581.
59. Joyce SA, MacSharry J, Casey PG *et al.* (2014) Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. *Proceedings of the National Academy of Sciences of the United States of America* **111**, 7421-7426.
60. Parseus A, Sommer N, Sommer F *et al.* (2017) Microbiota-induced obesity requires farnesoid X receptor. *Gut* **66**, 429-437.
61. Li F, Jiang C, Krausz KW *et al.* (2013) Microbiome remodelling leads to inhibition of intestinal farnesoid X receptor signalling and decreased obesity. *Nature communications* **4**, 2384.
62. Miettinen TA (1971) Cholesterol production in obesity. *Circulation* **44**, 842-850.
63. Nestel PJ, Schreibman PH, Ahrens EH, Jr. (1973) Cholesterol metabolism in human obesity. *J Clin Invest* **52**, 2389-2397.
64. Angelin B, Backman L, Einarsson K *et al.* (1982) Hepatic cholesterol metabolism in obesity: activity of microsomal 3-hydroxy-3-methylglutaryl coenzyme A reductase. *Journal of lipid research* **23**, 770-773.

581 65. Stahlberg D, Rudling M, Angelin B *et al.* (1997) Hepatic cholesterol metabolism in human obesity.
582 *Hepatology* **25**, 1447-1450.
583 66. Mamo JC, Watts GF, Barrett PH *et al.* (2001) Postprandial dyslipidemia in men with visceral
584 obesity: an effect of reduced LDL receptor expression? *Am J Physiol Endocrinol Metab* **281**, E626-
585 632.
586 67. Farrell GC, Larter CZ (2006) Nonalcoholic fatty liver disease: from steatosis to cirrhosis.
587 *Hepatology* **43**.
588 68. Wree A, Broderick L, Canbay A *et al.* (2013) From NAFLD to NASH to cirrhosis—new insights into
589 disease mechanisms. *Nature Reviews Gastroenterology and Hepatology* **10**, 627-636.
590 69. Moore JB, Gunn PJ, Fielding BA (2014) The role of dietary sugars and de novo lipogenesis in non-
591 alcoholic fatty liver disease. *Nutrients* **6**, 5679-5703.
592 70. Moore JB (2010) Non-alcoholic fatty liver disease: the hepatic consequence of obesity and the
593 metabolic syndrome. *Proc Nutr Soc* **69**, 211-220.
594 71. Moore JB (2019) From sugar to liver fat and public health: systems biology driven studies in
595 understanding non-alcoholic fatty liver disease pathogenesis. *Proc Nutr Soc*, 1-15.
596 72. Wang Z, Xu M, Peng J *et al.* (2013) Prevalence and associated metabolic factors of fatty liver
597 disease in the elderly. *Exp Gerontol* **48**, 705-709.
598 73. Bertolotti M, Lonardo A, Mussi C *et al.* (2014) Nonalcoholic fatty liver disease and aging:
599 epidemiology to management. *World J Gastroenterol* **20**, 14185-14204.
600 74. Loomba R, Abraham M, Unalp A *et al.* (2012) Association between diabetes, family history of
601 diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. *Hepatology* **56**, 943-951.
602 75. Cicero AFG, Gitto S, Fogacci F *et al.* (2018) Fatty liver index is associated to pulse wave velocity in
603 healthy subjects: Data from the Brisighella Heart Study. *Eur J Intern Med* **53**, 29-33.
604 76. Arguello G, Balboa E, Arrese M *et al.* (2015) Recent insights on the role of cholesterol in non-
605 alcoholic fatty liver disease. *Biochim Biophys Acta* **1852**, 1765-1778.
606 77. Ioannou GN (2016) The Role of Cholesterol in the Pathogenesis of NASH. *Trends Endocrinol*
607 *Metab* **27**, 84-95.
608 78. Tirosh O (2018) Hypoxic Signaling and Cholesterol Lipotoxicity in Fatty Liver Disease Progression.
609 *Oxid Med Cell Longev* **2018**, 2548154.
610 79. Van Rooyen DM, Larter CZ, Haigh WG *et al.* (2011) Hepatic free cholesterol accumulates in
611 obese, diabetic mice and causes nonalcoholic steatohepatitis. *Gastroenterology* **141**, 1393-1403,
612 1403.e1391-1395.
613 80. Seo E, Kang H, Choi H *et al.* (2019) Reactive oxygen species-induced changes in glucose and lipid
614 metabolism contribute to the accumulation of cholesterol in the liver during aging. *Aging Cell* **18**,
615 e12895.
616 81. Musso G, Gambino R, De Michieli F *et al.* (2003) Dietary habits and their relations to insulin
617 resistance and postprandial lipemia in nonalcoholic steatohepatitis. *Hepatology* **37**, 909-916.
618 82. Ioannou GN, Morrow OB, Connole ML *et al.* (2009) Association between dietary nutrient
619 composition and the incidence of cirrhosis or liver cancer in the United States population.
620 *Hepatology* **50**, 175-184.
621 83. Min HK, Kapoor A, Fuchs M *et al.* (2012) Increased hepatic synthesis and dysregulation of
622 cholesterol metabolism is associated with the severity of nonalcoholic fatty liver disease. *Cell Metab*
623 **15**, 665-674.
624 84. Claudel T, Staels B, Kuipers F (2005) The Farnesoid X receptor: a molecular link between bile acid
625 and lipid and glucose metabolism. *Arteriosclerosis, thrombosis, and vascular biology* **25**, 2020-2030.
626 85. Puri P, Daita K, Joyce A *et al.* (2017) The presence and severity of nonalcoholic steatohepatitis is
627 associated with specific changes in circulating bile acids. *Hepatology*.
628 86. Clemente-Postigo M, Queipo-Ortuno MI, Fernandez-Garcia D *et al.* (2011) Adipose tissue gene
629 expression of factors related to lipid processing in obesity. *PLoS One* **6**, e24783.
630 87. Kesaniemi YA, Grundy SM (1983) Increased low density lipoprotein production associated with
631 obesity. *Arteriosclerosis* **3**, 170-177.

88. Gerber PA, Nikolic D, Rizzo M (2017) Small, dense LDL: an update. *Curr Opin Cardiol* **32**, 454-459.
89. Kulanuwat S, Tungtrongchitr R, Billington D *et al.* (2015) Prevalence of plasma small dense LDL is increased in obesity in a Thai population. *Lipids Health Dis* **14**, 30.
90. Meyer BJ, Stewart FM, Brown EA *et al.* (2013) Maternal obesity is associated with the formation of small dense LDL and hypoadiponectinemia in the third trimester. *J Clin Endocrinol Metab* **98**, 643-652.
91. Denke MA, Sempos CT, Grundy SM (1993) Excess body weight. An underrecognized contributor to high blood cholesterol levels in white American men. *Arch Intern Med* **153**, 1093-1103.
92. Denke MA, Sempos CT, Grundy SM (1994) Excess body weight. An under-recognized contributor to dyslipidemia in white American women. *Arch Intern Med* **154**, 401-410.
93. Sternfeld B, Sidney S, Jacobs DR, Jr. *et al.* (1999) Seven-year changes in physical fitness, physical activity, and lipid profile in the CARDIA study. Coronary Artery Risk Development in Young Adults. *Ann Epidemiol* **9**, 25-33.
94. Lamon-Fava S, Wilson PW, Schaefer EJ (1996) Impact of body mass index on coronary heart disease risk factors in men and women. *Arteriosclerosis, thrombosis, and vascular biology* **16**, 1509-1515.
95. Shamai L, Lurix E, Shen M *et al.* (2011) Association of body mass index and lipid profiles: evaluation of a broad spectrum of body mass index patients including the morbidly obese. *Obes Surg* **21**, 42-47.
96. Garrison RJ, Wilson PW, Castelli WP *et al.* (1980) Obesity and lipoprotein cholesterol in the Framingham offspring study. *Metabolism* **29**, 1053-1060.
97. Ruan X, Li Z, Zhang Y *et al.* (2011) Apolipoprotein A-I possesses an anti-obesity effect associated with increase of energy expenditure and up-regulation of UCP1 in brown fat. *J Cell Mol Med* **15**, 763-772.
98. Sorrentino SA, Besler C, Rohrer L *et al.* (2010) Endothelial-vasoprotective effects of high-density lipoprotein are impaired in patients with type 2 diabetes mellitus but are improved after extended-release niacin therapy. *Circulation* **121**, 110-122.
99. Duong M, Uno K, Nankivell V *et al.* (2018) Induction of obesity impairs reverse cholesterol transport in ob/ob mice. *PLoS One* **13**, e0202102.
100. Arai T, Yamashita S, Hirano K-i *et al.* (1994) Increased plasma cholesteryl ester transfer protein in obese subjects. A possible mechanism for the reduction of serum HDL cholesterol levels in obesity. *Arteriosclerosis, Thrombosis, and Vascular Biology* **14**, 1129-1136.
101. Radeau T, Lau P, Robb M *et al.* (1995) Cholesteryl ester transfer protein (CETP) mRNA abundance in human adipose tissue: relationship to cell size and membrane cholesterol content. *Journal of lipid research* **36**, 2552-2561.
102. Li L, Hossain MA, Sadat S *et al.* (2011) Lecithin cholesterol acyltransferase null mice are protected from diet-induced obesity and insulin resistance in a gender-specific manner through multiple pathways. *Journal of Biological Chemistry* **286**, 17809-17820.
103. Morgan A, Mooney K, Wilkinson S *et al.* (2016) Investigating cholesterol metabolism and ageing using a systems biology approach. *Proceedings of the Nutrition Society*, 1-14.
104. Morgan A, Mooney KM, Wilkinson SJ *et al.* (2016) Cholesterol metabolism: A review of how ageing disrupts the biological mechanisms responsible for its regulation. *Ageing research reviews* **27**, 108-124.
105. Mc Auley MT, Mooney KM (2015) Computationally modeling lipid metabolism and aging: a mini-review. *Computational and structural biotechnology journal* **13**, 38-46.
106. Carroll MD, Lacher DA, Sorlie PD *et al.* (2005) Trends in serum lipids and lipoproteins of adults, 1960-2002. *Jama* **294**, 1773-1781.
107. Anderson KM, Wilson PW, Garrison RJ *et al.* (1987) Longitudinal and secular trends in lipoprotein cholesterol measurements in a general population sample. The Framingham Offspring Study. *Atherosclerosis* **68**, 59-66.

682 108. Criqui Mh, Frankville Dd, Barrett-Connor E *et al.* (1983) Change and correlates of change in high
683 and low density lipoprotein cholesterol after six years: a prospective study. *American journal of*
684 *epidemiology* **118**, 52-59.
685 109. Ettinger WH, Wahl PW, Kuller LH *et al.* (1992) Lipoprotein lipids in older people. Results from
686 the Cardiovascular Health Study. The CHS Collaborative Research Group. *Circulation* **86**, 858-869.
687 110. Morgan A, Mooney KM, Wilkinson SJ *et al.* (2016) Mathematically modelling the dynamics of
688 cholesterol metabolism and ageing. *Biosystems* **145**, 19-32.
689 111. Mc Auley MT, Wilkinson DJ, Jones JJ *et al.* (2012) A whole-body mathematical model of
690 cholesterol metabolism and its age-associated dysregulation. *BMC systems biology* **6**, 130.
691 112. Lee HC, Paz MA, Gallop PM (1982) Low density lipoprotein receptor binding in aging human
692 diploid fibroblasts in culture. *J Biol Chem* **257**, 8912-8918.
693 113. Kesaniemi YA, Grundy SM (1983) Increased low density lipoprotein production associated with
694 obesity. *Arteriosclerosis, Thrombosis, and Vascular Biology* **3**, 170-177.
695 114. Lamon-Fava S, Wilson PW, Schaefer EJ (1996) Impact of body mass index on coronary heart
696 disease risk factors in men and women. The Framingham Offspring Study. *Arterioscler Thromb Vasc*
697 *Biol* **16**, 1509-1515.
698 115. Aronne LJ, Brown WV, Isoldi KK (2007) Cardiovascular disease in obesity: A review of related risk
699 factors and risk-reduction strategies. *J Clin Lipidol* **1**, 575-582.
700 116. Kannel WB, Gordon T, Castelli WP (1979) Obesity, lipids, and glucose intolerance. The
701 Framingham Study. *The American journal of clinical nutrition* **32**, 1238-1245.
702 117. Laclaustra M, Lopez-Garcia E, Civeira F *et al.* (2018) LDL Cholesterol Rises With BMI Only in Lean
703 Individuals: Cross-sectional U.S. and Spanish Representative Data. *Diabetes Care* **41**, 2195-2201.
704 118. Cooney MT, Dudina A, De Bacquer D *et al.* (2009) HDL cholesterol protects against
705 cardiovascular disease in both genders, at all ages and at all levels of risk. *Atherosclerosis* **206**, 611-
706 616.
707 119. Heiss G, Tamir I, Davis CE *et al.* (1980) Lipoprotein-cholesterol distributions in selected North
708 American populations: the lipid research clinics program prevalence study. *Circulation* **61**, 302-315.
709 120. Flynn MA, Nolph GB, Baker AS *et al.* (1992) Aging in humans: a continuous 20-year study of
710 physiologic and dietary parameters. *Journal of the American College of Nutrition* **11**, 660-672.
711 121. Frishman WH, Ooi WL, Derman MP *et al.* (1992) Serum lipids and lipoproteins in advanced age.
712 Intraindividual changes. *Ann Epidemiol* **2**, 43-50.
713 122. Ferrara A, Barrett-Connor E, Shan J (1997) Total, LDL, and HDL cholesterol decrease with age in
714 older men and women. The Rancho Bernardo Study 1984-1994. *Circulation* **96**, 37-43.
715 123. Niemi T, Nikkila EA (1957) Effect of age on the lipemia clearing activity of serum after
716 administration of heparin to human subjects. *J Gerontol* **12**, 44-47.
717 124. Brodows RG, Campbell RG (1972) Effect of age on post-heparin lipase. *N Engl J Med* **287**, 969-
718 970.
719 125. Wang H, Eckel RH (2009) Lipoprotein lipase: from gene to obesity. *American Journal of*
720 *Physiology-Endocrinology and Metabolism* **297**, E271-E288.
721 126. Bertolotti M, Gabbi C, Anzivino C *et al.* (2007) Age-related changes in bile acid synthesis and
722 hepatic nuclear receptor expression. *Eur J Clin Invest* **37**, 501-508.
723 127. Welsh JA, Sharma A, Abramson JL *et al.* (2010) Caloric sweetener consumption and dyslipidemia
724 among US adults. *Jama* **303**, 1490-1497.
725 128. Schulze MB, Manson JE, Ludwig DS *et al.* (2004) Sugar-sweetened beverages, weight gain, and
726 incidence of type 2 diabetes in young and middle-aged women. *Jama* **292**, 927-934.
727 129. Haeusler RA, Camastra S, Nannipieri M *et al.* (2016) Increased Bile Acid Synthesis and Impaired
728 Bile Acid Transport in Human Obesity. *J Clin Endocrinol Metab* **101**, 1935-1944.
729 130. Harman D (1956) Aging: a theory based on free radical and radiation chemistry. *J Gerontol* **11**,
730 298-300.
731 131. Fernandez-Sanchez A, Madrigal-Santillan E, Bautista M *et al.* (2011) Inflammation, oxidative
732 stress, and obesity. *Int J Mol Sci* **12**, 3117-3132.

132. Fujita K, Nishizawa H, Funahashi T *et al.* (2006) Systemic oxidative stress is associated with visceral fat accumulation and the metabolic syndrome. *Circ J* **70**, 1437-1442.
133. Keaney JF, Larson MG, Vasan RS *et al.* (2003) Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. *Arteriosclerosis, thrombosis, and vascular biology* **23**, 434-439.
134. Mc Auley MT, Mooney KM (2017) LDL-C levels in older people: Cholesterol homeostasis and the free radical theory of ageing converge. *Medical Hypotheses* **104**, 15-19.
135. Pallottini V, Martini C, Bassi AM *et al.* (2006) Rat HMGCoA reductase activation in thioacetamide-induced liver injury is related to an increased reactive oxygen species content. *J Hepatol* **44**, 368-374.
136. Pallottini V, Martini C, Pascolini A *et al.* (2005) 3-Hydroxy-3-methylglutaryl coenzyme A reductase deregulation and age-related hypercholesterolemia: a new role for ROS. *Mech Ageing Dev* **126**, 845-851.
137. Pallottini V, Martini C, Cavallini G *et al.* (2007) Age-related HMG-CoA reductase deregulation depends on ROS-induced p38 activation. *Mechanisms of ageing and development* **128**, 688-695.
138. Singh RB, Mengi SA, Xu YJ *et al.* (2002) Pathogenesis of atherosclerosis: A multifactorial process. *Exp Clin Cardiol* **7**, 40-53.
139. Hollander D, Morgan D (1979) Increase in cholesterol intestinal absorption with aging in the rat. *Experimental gerontology* **14**, 201-204.
140. Duan LP, Wang HH, Ohashi A *et al.* (2006) Role of intestinal sterol transporters Abcg5, Abcg8, and Npc1l1 in cholesterol absorption in mice: gender and age effects. *Am J Physiol Gastrointest Liver Physiol* **290**, G269-276.
141. Shiomi M, Ito T, Fujioka T *et al.* (2000) Age-associated decrease in plasma cholesterol and changes in cholesterol metabolism in homozygous Watanabe heritable hyperlipidemic rabbits. *Metabolism: clinical and experimental* **49**, 552-556.
142. Camacho S, Ruppel A (2017) Is the calorie concept a real solution to the obesity epidemic? *Glob Health Action* **10**, 1289650.
143. Bray GA, Popkin BM (1998) Dietary fat intake does affect obesity! *The American journal of clinical nutrition* **68**, 1157-1173.
144. Subramanian S, Goodspeed L, Wang S *et al.* (2011) Dietary cholesterol exacerbates hepatic steatosis and inflammation in obese LDL receptor-deficient mice. *Journal of lipid research* **52**, 1626-1635.
145. Campos VC, Tappy L (2016) Physiological handling of dietary fructose-containing sugars: implications for health. *Int J Obes (Lond)* **40 Suppl 1**, S6-11.
146. Dong B, Singh AB, Azhar S *et al.* (2015) High-fructose feeding promotes accelerated degradation of hepatic LDL receptor and hypercholesterolemia in hamsters via elevated circulating PCSK9 levels. *Atherosclerosis* **239**, 364-374.
147. Stanhope KL, Bremer AA, Medici V *et al.* (2011) Consumption of fructose and high fructose corn syrup increase postprandial triglycerides, LDL-cholesterol, and apolipoprotein-B in young men and women. *J Clin Endocrinol Metab* **96**, E1596-1605.
148. Kohli R, Kirby M, Xanthakos SA *et al.* (2010) High-fructose, medium chain trans fat diet induces liver fibrosis and elevates plasma coenzyme Q9 in a novel murine model of obesity and nonalcoholic steatohepatitis. *Hepatology* **52**, 934-944.
149. Zhang X, Han J, Man K *et al.* (2016) CXC chemokine receptor 3 promotes steatohepatitis in mice through mediating inflammatory cytokines, macrophages and autophagy. *J Hepatol* **64**, 160-170.
150. Lakhan SE, Kirchgessner A (2013) The emerging role of dietary fructose in obesity and cognitive decline. *Nutr J* **12**, 114.
151. Goncalves Damascena K, Batisti Ferreira C, Dos Santos Teixeira P *et al.* (2017) Functional capacity and obesity reflect the cognitive performance of older adults living in long-term care facilities. *Psychogeriatrics* **17**, 439-445.

152. Cao D, Lu H, Lewis TL *et al.* (2007) Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease. *J Biol Chem* **282**, 36275-36282.
153. Mielke JG, Taghibiglou C, Liu L *et al.* (2005) A biochemical and functional characterization of diet-induced brain insulin resistance. *J Neurochem* **93**, 1568-1578.
154. Cisternas P, Salazar P, Serrano FG *et al.* (2015) Fructose consumption reduces hippocampal synaptic plasticity underlying cognitive performance. *Biochim Biophys Acta* **1852**, 2379-2390.
155. Martins IJ, Creegan R (2014) Links between insulin resistance, lipoprotein metabolism and amyloidosis in Alzheimer's Disease.
156. Vercalsteren E, Vranckx C, Frederix L *et al.* (2019) Advanced-age C57BL/6JRj mice do not develop obesity upon western-type diet exposure. *Adipocyte*, 1-9.
157. Maugeri A, Kunzova S, Medina-Inojosa JR *et al.* (2018) Association between eating time interval and frequency with ideal cardiovascular health: Results from a random sample Czech urban population. *Nutr Metab Cardiovasc Dis*.
158. Chen HJ, Chuang SY, Chang HY *et al.* (2019) Energy intake at different times of the day: Its association with elevated total and LDL cholesterol levels. *Nutr Metab Cardiovasc Dis* **29**, 390-397.
159. Brien SE, Ronksley PE, Turner BJ *et al.* (2011) Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *Bmj* **342**, d636.
160. Traversy G, Chaput JP (2015) Alcohol Consumption and Obesity: An Update. *Curr Obes Rep* **4**, 122-130.
161. Bessembinders K, Wielders J, van de Wiel A (2011) Severe hypertriglyceridemia influenced by alcohol (SHIBA). *Alcohol and alcoholism (Oxford, Oxfordshire)* **46**, 113-116.
162. Pownall HJ (1994) Dietary ethanol is associated with reduced lipolysis of intestinally derived lipoproteins. *Journal of lipid research* **35**, 2105-2113.
163. Bell H, Stromme JH, Steensland H *et al.* (1985) Plasma-HDL-cholesterol and estimated ethanol consumption in 104 patients with alcohol dependence syndrome. *Alcohol and alcoholism (Oxford, Oxfordshire)* **20**, 35-40.
164. Huang S, Li J, Shearer GC *et al.* (2017) Longitudinal study of alcohol consumption and HDL concentrations: a community-based study. *The American journal of clinical nutrition* **105**, 905-912.
165. Devenyi P, Robinson GM, Kapur BM *et al.* (1981) High-density lipoprotein cholesterol in male alcoholics with and without severe liver disease. *The American journal of medicine* **71**, 589-594.
166. Almeida OP, McCaul K, Hankey GJ *et al.* (2017) Excessive alcohol consumption increases mortality in later life: a genetic analysis of the health in men cohort study. *Addict Biol* **22**, 570-578.
167. Coulson CE, Williams LJ, Brennan SL *et al.* (2013) Alcohol consumption and body composition in a population-based sample of elderly Australian men. *Aging Clin Exp Res* **25**, 183-192.
168. You M, Fischer M, Deeg MA *et al.* (2002) Ethanol induces fatty acid synthesis pathways by activation of sterol regulatory element-binding protein (SREBP). *J Biol Chem* **277**, 29342-29347.
169. Rogers CQ, Ajmo JM, You M (2008) Adiponectin and alcoholic fatty liver disease. *IUBMB Life* **60**, 790-797.
170. Kharbanda KK, Todero SL, Ward BW *et al.* (2009) Betaine administration corrects ethanol-induced defective VLDL secretion. *Mol Cell Biochem* **327**, 75-78.
171. Nakanishi N, Yoshida H, Nakamura K *et al.* (2001) Influence of alcohol intake on risk for increased low-density lipoprotein cholesterol in middle-aged Japanese men. *Alcohol Clin Exp Res* **25**, 1046-1050.
172. Goodyear K, Lee MR, Schwandt ML *et al.* (2017) Hepatic, lipid and genetic factors associated with obesity: crosstalk with alcohol dependence? *World J Biol Psychiatry* **18**, 120-128.
173. Rautiainen S, Wang L, Lee IM *et al.* (2015) Higher Intake of Fruit, but Not Vegetables or Fiber, at Baseline Is Associated with Lower Risk of Becoming Overweight or Obese in Middle-Aged and Older Women of Normal BMI at Baseline. *J Nutr* **145**, 960-968.

174. Hebden L, O'Leary F, Rangan A *et al.* (2017) Fruit consumption and adiposity status in adults: A systematic review of current evidence. *Crit Rev Food Sci Nutr* **57**, 2526-2540.
175. Yu ZM, DeClercq V, Cui Y *et al.* (2018) Fruit and vegetable intake and body adiposity among populations in Eastern Canada: the Atlantic Partnership for Tomorrow's Health Study. *BMJ Open* **8**, e018060.
176. Bazzano LA (2008) Effects of soluble dietary fiber on low-density lipoprotein cholesterol and coronary heart disease risk. *Curr Atheroscler Rep* **10**, 473-477.
177. Brown L, Rosner B, Willett WW *et al.* (1999) Cholesterol-lowering effects of dietary fiber: a meta-analysis. *The American journal of clinical nutrition* **69**, 30-42.
178. Gunness P, Gidley MJ (2010) Mechanisms underlying the cholesterol-lowering properties of soluble dietary fibre polysaccharides. *Food Funct* **1**, 149-155.
179. He W-S, Zhu H, Chen Z-YJJoa *et al.* (2018) Plant Sterols: Chemical and enzymatic structural modifications and effects on their cholesterol-lowering activity. **66**, 3047-3062.
180. Katan MB, Grundy SM, Jones P *et al.* (2003) Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin Proc* **78**, 965-978.
181. Trautwein EA, Vermeer MA, Hiemstra H *et al.* (2018) LDL-Cholesterol Lowering of Plant Sterols and Stanols-Which Factors Influence Their Efficacy? *Nutrients* **10**.
182. Plat J, Baumgartner S, Vanmierlo T *et al.* (2019) Plant-based sterols and stanols in health & disease: "Consequences of human development in a plant-based environment?". *Prog Lipid Res* **74**, 87-102.
183. Li YC, Li CL, Li R *et al.* (2018) Associations of dietary phytosterols with blood lipid profiles and prevalence of obesity in Chinese adults, a cross-sectional study. *Lipids Health Dis* **17**, 54.
184. Cicero AFG, Fogacci F, Rosticci M *et al.* (2017) Effect of a short-term dietary supplementation with phytosterols, red yeast rice or both on lipid pattern in moderately hypercholesterolemic subjects: a three-arm, double-blind, randomized clinical trial. *Nutrition & metabolism* **14**, 61.
185. Zacek P, Bukowski M, Mehus A *et al.* (2019) Dietary saturated fatty acid type impacts obesity-induced metabolic dysfunction and plasma lipidomic signatures in mice. *J Nutr Biochem* **64**, 32-44.
186. Ronis MJ, Baumgardner JN, Sharma N *et al.* (2013) Medium chain triglycerides dose-dependently prevent liver pathology in a rat model of non-alcoholic fatty liver disease. *Exp Biol Med (Maywood)* **238**, 151-162.
187. St-Onge MP, Jones PJ (2002) Physiological effects of medium-chain triglycerides: potential agents in the prevention of obesity. *J Nutr* **132**, 329-332.
188. Phillips CM (2013) Metabolically healthy obesity: definitions, determinants and clinical implications. *Rev Endocr Metab Disord* **14**, 219-227.
189. Wildman RP, Muntner P, Reynolds K *et al.* (2008) The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). *Arch Intern Med* **168**, 1617-1624.
190. Achilike I, Hazuda HP, Fowler SP *et al.* (2015) Predicting the development of the metabolically healthy obese phenotype. *Int J Obes (Lond)* **39**, 228-234.
191. Banack HR, Kaufman JS (2013) The “obesity paradox” explained. *Epidemiology* **24**, 461-462.
192. Lavie CJ, De Schutter A, Milani RV (2015) Healthy obese versus unhealthy lean: the obesity paradox. *Nat Rev Endocrinol* **11**, 55-62.
193. Vierhapper H, Nardi A, Grosser P (2000) Prevalence of paradoxically normal serum cholestrol in morbidly obese women. *Metabolism* **49**, 607-610.
194. Dixon JB, O'Brien P (2001) A disparity between conventional lipid and insulin resistance markers at body mass index levels greater than 34 kg/m(2). *Int J Obes Relat Metab Disord* **25**, 793-797.
195. Da Cruz IB, Almeida MS, Schwanke CH *et al.* (2004) [Obesity prevalence among oldest-old and its association with risk factors and cardiovascular morbidity]. *Rev Assoc Med Bras (1992)* **50**, 172-177.

196. Bowman K, Delgado J, Henley WE *et al.* (2017) Obesity in Older People With and Without Conditions Associated With Weight Loss: Follow-up of 955,000 Primary Care Patients. *J Gerontol A Biol Sci Med Sci* **72**, 203-209.
197. Weverling-Rijnsburger AE, Jonkers IM, van Exel E *et al.* (2003) High-density vs low-density lipoprotein cholesterol as the risk factor for coronary artery disease and stroke in old age. *Archives of Internal Medicine* **163**, 1549-1554.
198. Ravnskov U, Diamond DM, Hama R *et al.* (2016) Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ open* **6**, e010401.
199. Al-Mallah MH, Hatahet H, Cavalcante JL *et al.* (2009) Low admission LDL-cholesterol is associated with increased 3-year all-cause mortality in patients with non ST segment elevation myocardial infarction. *Cardiol J* **16**, 227-233.
200. Lv YB, Yin ZX, Chei CL *et al.* (2015) Low-density lipoprotein cholesterol was inversely associated with 3-year all-cause mortality among Chinese oldest old: data from the Chinese Longitudinal Healthy Longevity Survey. *Atherosclerosis* **239**, 137-142.
201. Formiga F, Ferrer A, Sanz H *et al.* (2013) Patterns of comorbidity and multimorbidity in the oldest old: the Octabaix study. *Eur J Intern Med* **24**, 40-44.
202. Dai D-F, Chiao YA, Marcinek DJ *et al.* (2014) Mitochondrial oxidative stress in aging and healthspan. *Longevity & healthspan* **3**, 6.
203. Mc Auley MT (2018) The Interplay Between Cholesterol Metabolism and Intrinsic Ageing. *Subcell Biochem* **90**, 99-118.
204. Zhao L, Chen Y, Tang R *et al.* (2011) Inflammatory stress exacerbates hepatic cholesterol accumulation via increasing cholesterol uptake and de novo synthesis. *J Gastroenterol Hepatol* **26**, 875-883.
205. Francque SM, van der Graaff D, Kwanten WJ (2016) Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications. *Journal of hepatology* **65**, 425-443.
206. Dulai PS, Singh S, Patel J *et al.* (2017) Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. *Hepatology* **65**, 1557-1565.

## List of Figures

**Figure 1:** Overview of whole-body cholesterol metabolism. Cholesterol metabolism is maintained by an array of regulatory processes which control absorption, synthesis, hepatic lipoprotein production, lipoprotein uptake and reverse cholesterol transport. The signs indicate where obesity has been shown to impact cholesterol metabolism. Note: cholesterol absorption has both a positive and negative sign associated with it, to indicate that certain studies have found that obesity decreases cholesterol absorption while other have found the opposite effect. Abbreviations: ABCA1, ATP-binding cassette transporter; Acetyl-CoA, acetyl coenzyme A; ABCG5/G8, ATP-binding cassette (ABC) transporters G5 and G8; ACAT2, acetyl CoA acetyltransferase 2; CETP, cholesteryl ester transfer protein; CYP7A1, cholesterol 7 alpha-hydroxylase; IDL, intermediate density lipoprotein; HDL, high density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HMGCR, HMG-CoA reductase; LCAT, lecithin–cholesterol acyltransferase; LDL, low density lipoprotein; NPC1L1, Niemann-Pick C1-Like 1; PCSK9, proprotein convertase subtilisin/kexin type 9; SCAP, sterol regulatory element-binding

926 protein cleavage-activating protein; SREBP-2, sterol regulatory element-binding protein 2; scavenger
927 receptor, class B type 1(SR-B1); VLDL, very low density lipoprotein.
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929
930 **Figure 2:** Conceptual model of obesity/ageing induced changes to hepatic cholesterol metabolism
931 which could result in low levels of LDL-C. A metabolic feature which has been observed in a number
932 of studies involving the oldest old. Abbreviations: Acetyl-CoA, acetyl coenzyme A; ACAT2, acetyl
933 CoA acetyltransferase 2; CETP, cholesteryl ester transfer protein; CYP7A1, Cholesterol 7 alpha-
934 hydroxylase; IDL, intermediate density lipoprotein; HDL, high density lipoprotein; HMG-CoA, 3-
935 hydroxy-3-methylglutaryl-CoA; HMGCR, HMG-CoA reductase; LCAT, lecithin–cholesterol
936 acyltransferase; LDL, low density lipoprotein; MUHO, metabolically unhealthy obese; ROS, reactive
937 oxygen species; SREBP-2,scavenger receptor, class B type 1(SR-B1); VLDL, very low density
938 lipoprotein.