OSLOMET

Master's Thesis

Master's Programme in Public Health Nutrition.

August, 2022

The association between estimated hepatic SCD-1 enzyme activity and overweight and obesity.

A literature review of published scientific research studies.

Nina Wærstad Palmer

Course code: MAME5910

Faculty of Health Sciences

PREFACE

The topic of this master's thesis was suggested to me from researchers at the University of Oslo. It immediately caught my interest since I from experience know how influential body weight and its related health problems can become in a person's life.

It has both been a challenging and rewarding journey and has certainly become the most defining years of my life, both professionally and personally. Along the way I have broken a hip and a shoulder, experienced Corona lock-down, and then just before submission, the sudden loss of my father.

It has certainly been a period I have had to grow through. Hopefully, I come out at the other end as a more insightful person. I take everything I have learnt with me and look forward to future projects. The rewarding experience of suddenly understanding something after having investigated it again and again is certainly one of the most valuable experiences from this project.

My sincere thanks to my impressive friends Marit Gamst Markussen and Camilla Sanne Huseby, for your time and availability and relentless support and encouragement throughout the entire process. I am so grateful to know you and admire the both of you tremendously. You are wonderful people. My sincere thanks also to the administration at the Faculty of Health Sciences. You were tremendously helpful, supportive, and understanding.

Finally, I dedicate this thesis to my father. You said I would make it and succeed in the end. Thank you for everything you gave me. I will for always carry you in my heart.

ABSTRACT

ENGLISH

Introduction: Stearoyl Co-A desaturase (SCD-1) has an essential role in the human fatty acid metabolism as a rate limiting enzyme that ensures the synthesis of monounsaturated fatty acids from saturated fatty acids. Changes in fatty acid composition and hepatic SCD-1 activity have been found to be associated with overweight and obesity as well as disproportionate and abnormal body fat accumulation. The aim of this thesis was to perform a literature review of human studies investigating these associations.

Methods: A literature search was performed in PubMed to identify relevant studies. A set of predefined selection criteria were used to determine inclusion.

Results: Variations in estimated SCD-1 activity were found to be associated with BMI in most of the included studies, but also varied in response to anthropometric indicators reflecting body fat distribution. Differences in SCD-1 estimates were found despite similar BMI and similar estimates were found despite different BMI. The SCD-1 enzyme's activity was also found to be associated with other variables measuring metabolic health, especially insulin regulation.

Conclusion: Data on SCD-1 activity in overweight and obesity need to be interpreted and understood in a larger context than the influence of excess body mass. Alterations in SCD-1 activity, and especially a high SCD16 index, may be a symptom of chronic overnutrition and high hepatic lipogenesis as well as central obesity, excessive liver fat and/or metabolic stress. However, a high SCD-1 activity has also been found to be conducive in the preservation of metabolic health. When considering a possible association between SCD-1 estimates and BMI it appears necessary to consider additional anthropometric and metabolic health indicators. Due to the large variation in thematic orientation, study design and subject characteristics of the included articles it was difficult to compare results. No firm conclusions regarding the SCD-1 enzyme's role and influence in excessive and abnormal body fat storage may be drawn, and more research is necessary.

NORSK

Introduksjon: Enzymet Stearoyl Co-A desaturase (SCD-1) har en fundamentalt viktig rolle i fettsyremetabolismen i menneskekroppen. SCD-1 katalyserer omdannelsen av mettede til enummetede fettsyrer. Endringer i fettsyresammensetningen og enzymets aktivitet i leveren har blitt assosiert med overvekt og fedme samt ugunstig kroppssammensetning og unormal lagring av kroppsfett. Hensikten med denne oppgaven var å foreta en litteratur studie for å undersøke disse assosiasjonene.

Metode: Ett litteratur søk etter relevante studier ble foretatt i PubMed. Ett sett forhåndsdefinerte utvalgskriterier ble benyttet for å avgjøre om studien kvalifiserte til å bli inkludert.

Resultater: De fleste av de inkluderte studiene fant en assosiasjon mellom estimert SCD-1 aktivitet og BMI, men enzymet varierte også med antropometriske indikatorer som er egnet til å reflektere kroppssammensetning og økt fettlagring i visse deler av kroppen. Det var eksempler på studier som fant ulikheter i SCD-1 aktivitet på tross av lik BMI, samt studier som fant lik SCD-1 til tross for ulik BMI. SCD-1 enzymets aktivitet ble også funnet å være assosiert med andre mål på metabolsk helse, spesielt insulin regulering.

Konklusjon: For å forstå og tolke SCD-1 enzymets aktivitet i forbindelse med overvekt og fedme kan det være nødvendig å se SCD-1 aktiviteten i en større sammenheng enn graden av økt kroppsmasse. Forhøyede nivåer av SCD-1 estimater, og spesielt SCD16, kan være en indiksjon på en kronisk positiv energibalanse, økt lipogenese samt abdominal fedme, lever fett og metabolske forstyrrelser. Enzymet kan imidlertid også være forhøyet i en velfungerende kropp og bidra til å bevare god metabolsk helse. I vurderingen av en mulig assosiasjon mellom SCD-1 og BMI ser det ut til å være nødvendig å også ta i betraktning andre mål for kroppsfett som større grad reflekter fettfordelingen og spesielle fettansamlinger i kroppen. Som følge av de store variasjonene i tematisk vektlegging, studiedesign og deltagernes kjennetegn var det ikke mulig å komme med sterke konklusjoner, og det er behov for mer forskning på området.

Contents

ABBREVIATIONS

AI	Anthropometric indicator
AHI	Anthropometric health indicator
ALT	Alanine aminotransferase
AT	Adipose tissue
AT-TAG	Adipose tissue triglycerides
BF	Body fat
BF%	Body fat percentage
BMI	Body mass index
BP	Blood pressure
CE	Cholesterol ester
D5D	Delta-5 desaturase
D6D	Delta-6 desaturase
DEXA	Dual-energy X-ray absorptiometry
DHA	Docosahexaenoic acid
CVD	Cardiovascular diseases
DNL	De novo lipogenesis
FA	Fatty acid
FM	Fat mass
FM%	Fat mass percentage
HOMA-IR	Homeostasis model assessment insulin resistance
IR	Insulin resistance
L1 and L4	Lumbar vertebrae 1 and lumbar vertebrae 4
LA	Linoleic acid
LF	Liver fat
MetS	Metabolic syndrome
MH	Metabolically healthy
MHI	Metabolic health indicator
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid

MU	Metabolically unhealthy
MUFA	Monounsaturated fatty acid
n-3	Omega-3
n-6	Omega-6
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis (pathological levels of liver fat)
NW	Normal weight
OA	Oleic acid
OB	Obese
OR	Odds ratio
OW	Overweight
PA	Palmitic acid
PAL	Palmitoleic acid
PC	Phosphatidylcholines
PL	Phospholipids
POW	Percentage overweight
PUFA	Polyunsaturated fatty acid
RBC	Red blood cell
RBC PL	Red blood cell phospholipids
SA	Stearic acid
SAD	Sagittal abdominal diameter
SAT	Subcutaneous adipose tissue
SCD	Stearoyl-coenzyme A desaturase gene
SCD-1	Stearoyl-coenzyme A desaturase 1
SCD16	Stearoyl-coenzyme A desaturase 1 estimated by finding the fatty acid ratio of palmitoleic acid (PAL) to palmitic acid (PA)
SCD18	Stearoyl-coenzyme A desaturase 1 estimated by finding the fatty acid ratio of oleic acid (OA) to stearic acid (SA)
SD	Standard deviation
SFA	Saturated fatty acid
SOB	Severely obese

SREBP-1	Sterol regulatory element binding transcription factor 1
T2D	Type 2 diabetes
TGR	Triglyceride
VAT	Visceral adipose tissue
VF	Visceral fat
VLDL	Very-low-density lipoprotein
VLDL-TGR	Very-low-density lipoprotein triglyceride
VLCD	Very low carbohydrate diet
WC	Waist circumference
WHR	Waist-to-hip ratio
WtHR	Waist-to-hight ratio

INTRODUCTION

Overweight and obesity have reached epidemic proportions in most nations and regions across the globe. The situation has been referred to as a pandemic, growing in magnitude and seriousness in developed and developing countries alike (Santosh Kumar, Bhat & Sorake, 2021). On a global level obesity tripled between 1975 and 2016 (WHO, 2021). The prevalence of obesity is still rising in most areas across globe, and particularly among children and young adults (WHO, 2022). These problems occupy both public and private health service capacity, and result in personal suffering as well as increasing public health expenditure (WHO, 2022). In 2020 the world faced an infectious pandemic, a pandemic that revealed that the additional vulnerability for health problems implicated in overweight and obesity is not limited to so-called lifestyle related diseases, but also are relevant when facing communicable diseases.

Overweight and obesity as estimated by the body mass index (BMI) is an often applied and widely accepted tool to refer to and discuss the extent of elevated body weight and body fat. Using a person's height and weight, a person's body mass may be determined and sorted in three predefined categories; overweight is defined as having a BMI between 25 and 29.9 kg/m2 and obesity as having a BMI of 30 kg/m2 or higher (Vinknes, 2014, p. 9). Obesity may be further divided into various categories reflecting obesity severity.

The BMI ranges are based on the effect excessive body fat has been found to have on health, disease and death (WHO, 2022; Nuttall, 2015). Even slight weight loss has been found to significantly reduce the risk for health problems related to body fatness (Guh et al., 2009; Aune et al. 2016; Araújo, Cai & Stevens, 2019). However, findings in scientific studies regarding the physical consequences of excess BMI are conflicting. Measured by BMI, some apparently remain healthy even after becoming classified as obese, while others appear to suffer metabolically due to adipose tissue related disturbances already at a normal BMI (Svendsen et al., 2021; Rondanelli et al., 2015; Ojwang et al., 2020).

Several epidemiological studies have investigated the physiological processes leading to overweight and obesity. Possible associations with changes in circulating fatty acid (FA) composition have been suggested and observed (Warensjø, Ohrvall & Vessby, 2006; Kishino et al., 2008; Vinknes et al., 2013; Rosqvist et al., 2017). FAs execute essential biological

effects through different molecular mechanisms (Vinknes, 2014 p. 14). Metabolic regulation involves the continuously ongoing physiological process of utilisation and storage of available energy. The liver is closely involved in this process, a process that enables maintaining metabolic functioning and homeostasis despite variations in supply and demand of nutrients. The liver is the central metabolic organ in metabolic lipid homeostasis (Alves-Bezerra & Cohen, 2017).

Human FA composition is affected by the diet, but also by the internal (endogenous) processing of fat (Warensjø et al., 2009; Rondanelli et al., 2015; Hlavaty et al, 2015; Vinknes, 2014, p. 17). In addition to lipolysis (release of FFA from adipose tissue) in the fasted state and de novo lipogenesis (DNL) in the fed state, this involves the desaturation and elongation of FAs. Elongases elongate SFAs by incorporating additional carbon units, whereas desaturases introduce double bonds in the cell membrane, and hence transform the SFA into an unsaturated FA (Vinknes, 2014, p. 17).

Stearoyl-CoA desaturase (SCD), also referred to as Delta-9 desaturase, is an essential metabolic enzyme in the body's endogenous synthesis of monounsaturated fatty acids (MUFAs) (Murata and Wada, 1995).) It catalyses the rate-limiting step in the conversion of the SFA palmitic acid (PA) (16:0) and stearic acid (SA) (18:0) to the MUFAs palmitoleic acid (PAL) (16:1) and oleic acid (OA) (C18:1) respectively (Figure I and Figure II (enclosures)). In addition to adipose tissue, the SCD-1 enzyme is believed to be especially active in the liver (Vinknes, 2014, p. 18).

The calculation and analysis of desaturation activity estimates is often split into the SCD16 and SCD18 activity index to reflect the two main metabolic pathways starting from PA and SA respectively (Bonafini et al., 2020). For SCD16 this involves finding the ratio of palmitoleic acid (PAL) 16:1n-7 to palmitic acid (PA) 16:0, and for SCD18 the ratio of oleic acid (OA) 18:1n-9 to stearic acid (SA) 18:0. The SCD16 index reflects the site-specific insertion of a double bond instead of a single bond between carbons 7 and 8 of PA in the synthesis of PAL, and the SCD18 index reflects the insertion of a single bond between carbons 9 and 10 of SA in the synthesis of OA (Ntambi & Miyazaki, 2004).

The rationale behind estimating SCD-1 activity by calculating ratios is that the SCD-1 enzyme is regulated according to a feedback loop (i.e., follow a feedback regulation) based on the

availability of its substrates and products (Flowers & Ntambi 2008; Schiller et al., 2014; Bonafini et al. 2020). High availability of the substrates PA and SA respectively may indicate increased activity of the SCD-1 enzyme. High hepatic SCD-1 activity estimates have been found to be associated with overweight and obesity (Warensjø et al., 2006; Warensjø et al., 2009; Vinknes et al., 2013; Bonafini et al., 2020; Adlago et al., 2017; Morcillo et al., 2017).

Hepatic SCD-1 enzyme activity cannot be exactly determined without performing invasive, costly as well as time- and labour consuming biopsies. For this reason, it has in large scale epidemiological research and clinical practise been investigated whether the enzyme's activity may instead be accurately determined by estimating its expression in FA ratios. SCD-1 activity ratios may be calculated from the FA composition measured in total lipids (whole blood, serum or plasma) or specific lipid fractions (phospholipids (PLs), cholesterol esters (CEs), triglycerides (TGRs), total very-low-density lipoprotein (VLDL) or erythrocytes (red blood cells)) extracted from standard blood samples. Calculations based on haematological data from the circulating bloodstream FA composition have been argued to primarily reflect hepatic metabolism (Peter et al., 2009). If hepatic SCD-1 estimates are reliable and valid, variations in FA composition and estimated SCD-1 activity may be useful when investigating if the SCD-1 enzyme may be associated with physiological processes contributing to or resulting in overweight and obesity.

De novo lipogenesis (DNL) involves the process where excess carbohydrates are transformed into SFA, and primarily so PA. The following endogenous processes regulated by the SCD-1 enzyme involves the desaturation of these saturated fatty acids (SFAs) into monounsaturated fatty acids (MUFAs) (Chong et al., 2008; Silbernagel et al., 2012; Lee et al., 2015; Rosqvist et al., 2019b). The process of DNL primarily occurs in the liver, but also takes place in adipose tissue) (Vinknes, 2014, p. 17).

The amount of circulating PA can reflect either high intake dietary SFAs or process of DNL whereas a high SCD16 and PAL in the body may reflect a high SCD-1 enzyme. Hepatic FA composition and estimated SCD-1 will also be influenced by adipose tissue lipolysis (Peter et al., 2009). When SFAs are high, the SCD-1 enzyme performs an essential role to ensure the FA composition necessary for the assembly of VLDL particles, which transport triglycerides (TGR) from the liver to adipose tissue (AT) and other tissues or organs (Stefan et al., 2008;

Kishino et al., 2008; Peter et al., 2009; Collins, Neville, Hoppa & Frayn, 2010; Alves-Bezerra & Cohen, 2017).

The role and influence of hepatic SCD-1 activity in human lipid metabolism and fat storage remains a frequent topic in epidemiological research. The SCD-1 enzyme performs essential tasks to preserve a well-functioning metabolism in the human body (i.e., the utilisation and storage of available energy), and has been found to be implicated in the regulation of FA storage and distribution. This emphasises the importance of further elucidating a possible association between the regulation and functions of the SCD-1 enzyme in and overweight and obese state.

Aim

The aim of this thesis was to perform a literature study of human studies investigating a possible association between estimated hepatic SCD-1 enzyme activity and overweight and obesity as well as disproportionate and abnormal body fat accumulation.

RESEARCH METHODS

A literature search for eligible studies was carried out in PubMed. The search procedure was completed on the 28th of January 2020.

Four searches were performed based on the following keywords: 1. “SCD-1 AND overweight”, 2. “SCD-1 AND obesity”, 3. “Stearoyl Coenzyme Desaturase AND overweight” and 4. “Stearoyl Coenzyme Desaturase AND obesity”. Substituting “SCD-1” and “Stearoyl Coenzyme Desaturase” with “Desaturase 9” did not provide any additional relevant studies. The following two filters were applied in the searches: 1. Human studies and 2. English language only.

When the four searches had been completed, the following selection criteria were used to determine inclusion (Figure 1):

1. Included participants with a BMI at or above 25. The study qualified for inclusion if BMI was sufficiently high when the deviation of individual values from the mean value was considered.

2. No reviews, only original research articles.

3. No experimental cell studies or animal studies.

4. Not being obviously thematically irrelevant.

5. Included estimates of SCD16 and/or SCD18 activity calculated from circulating lipids in the blood stream.

6. No pharmacological studies.

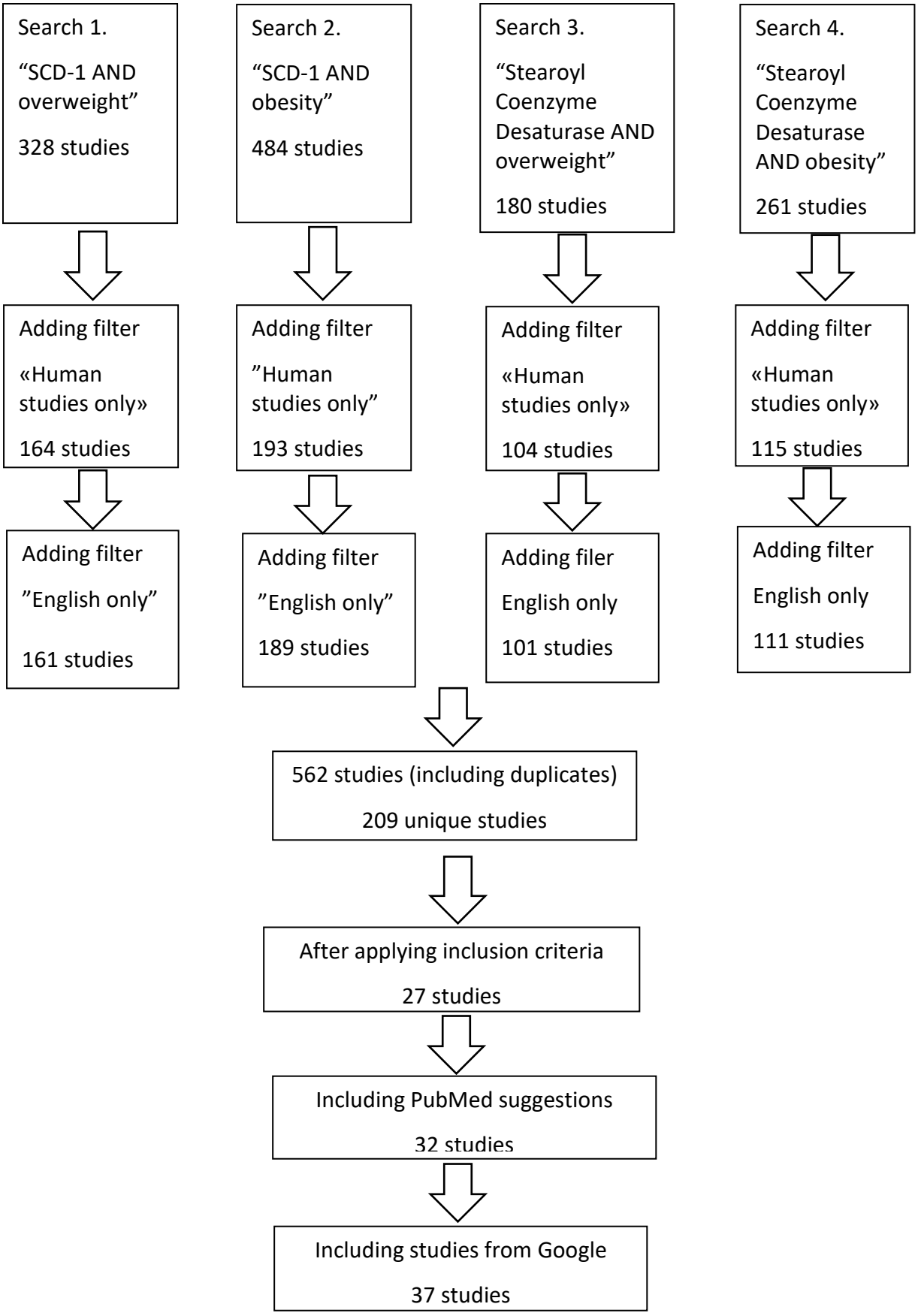

Figure 1. Flow chart of literature search and included studies.

When all four searches had been completed and the duplicates removed, I was left with 209 unique articles to be evaluated according to the eligibility criteria. Despite having applied a filter in the literature search, many animal and experimental studies had been included and were consequently removed. Similarly, many obviously thematically irrelevant articles had to be removed. There were also some clearly relevant studies that had to be removed because they used PAL as an expression of SCD16 activity (instead of estimating SCD16 activity by calculating the ratio of PAL/PA).

After having evaluated all the studies from the search result according to the selection criteria, 26 studies were left for inclusion in the analysis. Five additional articles (Kishino et al., 2008; Aglalgo et al., 2017; Rosqvist et al., 2017; Yammine et al., 2018 and Ojwang et al. 2020) were added while working on evaluating the studies included on the list from the literature search. They were suggestions of similar articles made by PubMed and were added due to their relevance. In addition, independent searches were conducted on Google using the same search terms that were applied on PubMed. In this way an additional six articles (Rondanelli et al., 2015; Zeman et al., 2017; Del Pozo et al., 2020; Svendsen et al., 2020; Jauregibeitia et al., 2020 and Bonafini et al., 2020) came to my awareness.

The entire literature search process rendered a total of 37 studies to be included in the result. To quality check the result, a literature search following an identical procedure was performed in Ovid together with a librarian. This did not render any new articles.

Due to the importance of the liver in human FA metabolism and the SCD-1 enzyme's high expression in the liver (Frayn, 2010, p. 92 and Vinknes, 2014, p. 18), SCD-1 activity in the liver was chosen as the focus in this literature review. As such it is the association between estimated SCD-1 activity calculated from measurements of the haematologic FA composition in the circulating blood stream that will be analysed and discussed. Compared to SCD-1 ratios calculated based on adipose tissue FA composition, lipids extracted from the blood provide a more accurate and recent reflection of hepatic SCD-1 activity. They are as such more able to reflect endogenous liver metabolism (Vessby et al, 2002; Warensjø et al., 2009; Gustafsson, Tengblad, Boberg & Andersson, 2002). Studies based on SCD-1 activity taken from adipose tissue FA composition did not qualify for inclusion. Even though the central focus of this project is the association between body fatness and SCD-1 liver metabolism

however, processes occurring in adipose tissue will be mentioned since the body operates as an interconnected system.

In addition to BMI, it will be referred to other anthropometric indicators (AIs). Waist Circumference (WC) and Waist-to-Hight Ratio (WtHR) will be regarded as indicators of abdominal fat and body fat distribution whereas Waist-to-Hip ratio (WHR), Visceral adipose tissue (VAT) and Sagittal Abdominal Diameter (SAD) will be regarded as indicators of visceral fat (Piqueras et al., 2017). The reliability and validity of these indicators will not be discussed.

If the mean BMI was within the normal weight (NW) category but included overweight (OW) participants due to the range or the standard deviation, the study qualified for inclusion if correlation analysis investigating associations between estimated SCD-1 activity and BMI and/or abdominal obesity had been performed.

Two of the studies that had children as their study population had used alternative indicators to BMI (relative weight by Abe et al., 2012 and percentage overweight by Saito et al., 2014). Because they are based on the same principle as BMI (calculated from the persons height and weight) and in practise are identical to the BMI index (Gray & Fujioka, 1991), they were included.

RESULTS

All of the 37 included studies investigated if estimates of the SCD-1 enzyme's activity could help to explain and elucidate the enzyme's role and influence on the physiological processes involved in body mass regulation, adipose tissue distribution and general metabolic health. The primary aim varied however between the different studies, some focusing on the enzyme's possible association with overweight and obesity whereas the influence of abdominal obesity, liver fat and metabolic health was the focus in others.

Among the 37 studies, there were 22 cross-sectional studies, six case-control studies with cross-sectional data and nine case-control studies with prospective longitudinal data (Warensjø et al., 2005; Stefan et al., 2008; Abe et al., 2012; Silbernagel et al., 2012; Choi et al., 2014; Wolters et al., 2015; Rondanelli et al., 2015; Morcillo et al., 2017 and Lee et al., 2018).

Table 1 lists the included studies' findings regarding associations between hepatic SCD-1 estimates and overweight and obesity defined by BMI, as well as findings regarding lipid accumulation according to AIs reflecting body fat distribution and excessive liver fat accumulation. A more comprehensive table on findings, demographic variables and study specific definitions is included in Table III, IV and V in the enclosures section.

Table1. Significant associations between estimated enzymatic SCD-1 activity and overweight or obesity according to various anthropometric indicators

Study	Population BMI	Association with BMI	Associations with other anthropometric indicators
1. Associations Among Fatty Acids, Desaturase and Elongase, and Insulin Resistance in Children, Beccarelli et al., 2018.	NW OW OB	SCD16: No association SCD18: No association	SCD16: No association SCD18: No association
2. Association of Plasma Lipids Fatty Acid Composition with Metabolic Profile of Czech Adolescents, Hlavaty et al., 2015.	NW OW OB	SCD16: No significant association SCD18: No association.	BF% SCD16: Significant positive association SCD18: Not associated.
3. Plasma palmitoleic acid content and obesity in children, Okada et al., 2005.	NW OB	SCD16: Significant positive association	WHR SCD16: Significant positive association BF%: SCD16: Positive association, but not significant.
4. Associations Between Estimated Desaturase Activity and Insulin Resistance in Korean Boys, Choi et al., 2014.	NW OW OB	SCD 16 Baseline total population: Significant positive association Follow-up: Significant positive association disappeared, but remained when the OW and OB were compared to the NW. SCD 18 No significant association, but negative direction.	WC SCD16: Baseline: Significant positive association Follow-up: Significant positive association disappeared, but remained when the OW and OB were compared to the NW. SCD18: No significant association, but negative direction.
5. Association of Changes in Body Fatness and Fatty Acid Composition of Plasma	NW OB	POW SCD16: No association SCD18	WHtR SCD16:No association SCD18

Phospholipids during early Puberty in Japanese Children, Abe, 2012.		Baseline: Significant negative association among boys.	Baseline: Significant negative association among boys.
6. Changes in SCD gene DNA methylation after bariatric surgery in morbidly obese patients are associated with free fatty acids, Morcillo et al., 2017	OB SOB	SCD16: Significant positive association. SCD18: Significant positive association.	<u>WC</u> SCD16: Significant positive association SCD18: Significant positive association
7. Association between increased visceral fat area and alterations in plasma fatty acid profile in overweight subjects: a cross-sectional study, Kang et al., 2017.	OW	SCD16: No significant association SCD18: No significant association	<u>VAT</u> SCD16: Significant positive association SCD18: Significant positive association
8. Desaturase Activity Is Associated With Weight Status and Metabolic Risk Markers in Young Children, Wolters et al., 2015.	NW OW OB	SCD16 -Significant positive association both at baseline and follow-up. -SCD16 did not have a significant predictive power on BMI at follow-up.	
9. Serum phospholipid and cholesteryl ester fatty acids and estimated desaturase activities are related to overweight and cardiovascular risk factors in adolescents, Steffen et al., 2008.	NW OW	SCD16 -Bivariate analysis: Significant positive association in CE, but not in PL. -Significance lost in multiple regression analysis together with cardiometabolic risk factors.	SCD16 <u>WC</u> Not significantly associated in multiple regression analysis together with other cardiometabolic risk factors
10. Effects of two-months balanced diet in metabolically healthy obesity: lipid correlations with gender and BMI-related differences, Rondanelli et al., 2015.	OW OB	SCD16: No significant association SCD18: Significant negative association at baseline An intervention and significant reduction in BMI did not change activity estimates.	<u>Android FM</u> SCD16 and SCD18: An intervention and significant reduction in android FM did not change activity estimates.

11. Docosahexaenoic Acid Content in Plasma Phospholipids and Desaturase Indices in Obese Children, Saito et al., 2011.	OW	SCD16: Significant positive association SCD18: Significant positive association	<u>WHtR</u> SCD16: Significant positive association SCD18: No association, but positive direction
12. Relationship between estimated fatty acid desaturase activities and abdominal adiposity in Japanese children, Saito et al., 2014.	NW OW	SCD18 POW: Potential association	<u>WHtR</u> SCD18: U-shaped association since both children with and without high WHtR had high SCD18 activity estimates.
13. Fatty Acid Composition of Plasma Phosphatidylcholine Determines Body Fat Parameters in Subjects with Metabolic Syndrome-Related Traits, Zeman et al., 2017.	NW OW	SCD16: Potential significant positive association SCD18: Not significantly associated, but negative direction.	<u>FM</u> SCD16: Potential negative association <u>WC</u> SCD18: Potential negative association
14. Association between serum phospholipid fatty acid levels and adiposity in Mexican women, Aglago et al., 2017.	OB	SCD16: Significant positive association SCD18 Significant negative association, significance lost when tested for false discovery rate.	<u>WC</u> SCD16 Significant positive association SCD18 Significant negative association, significance lost when tested for false discovery rate. <u>WHR:</u> SCD16 Positive association, not significant. SCD18 Not associated
15. Comparison of dietary and plasma phospholipid fatty acids between normal weight and overweight black South Africans	NW OW OB	<u>SCD16</u> Within BMI-groups: Positive association (NW) Significant positive association (OB) Between BMI groups:	SCD16 and SCD18 <u>WC</u> Potential significant positive association <u>WtHR</u> Potential significant positive association

according to metabolic health: The PURE study, Ojwang, 2020.		Significant negative association SCD18 Within BMI-groups: Significant positive association Between BMI groups: Significant negative association	Metabolic health Negatively associated
16. Plasma lipid fatty acid composition, desaturase activities and insulin sensitivity in Amerindian women, Vessby et al., 2012.	NW OW	SCD16 Significant positive association SCD18 Not estimated	FM SCD16 Significant positive association among the women from Lima, but not the women from the Shuar region.
17. Serum Phospholipid Fatty Acids Levels, Anthropometric Variables and Adiposity in Spanish Premenopausal Women, del Pilar del Pozo et al., 2020.	NW OW	SCD16 Significant positive association SCD18 Significant negative association	VAT and BF% SCD16 No significant association. WC SCD18 Significant positive association.
18. Effect of weight loss on circulating fatty acid profiles in overweight subjects with high visceral fat area: a 12-week randomized controlled trial, Lee et al., 2018.	OW	SCD16 Significant positive association SCD18 Not associated	VAT SCD16 Weak positive association SCD18 Not associated
19. Plasma palmitoleic acid, a product of stearoyl-CoA desaturase activity, is an independent marker of triglyceridemia and abdominal adiposity, Paillard et al., 2008	NW OW	SCD16 Significant positive association, but possibly secondary to circulating TGR levels and/or abdominal obesity.	WC SCD16 Significant positive association, but possibly secondary to circulating TGR levels.
20.	NW OW	SCD16	

Fatty acid profile and estimated desaturase activities in whole blood are associated with metabolic health, Svendssen et al., 2020.	OB	No association independent of metabolic health SCD18 No association independent of metabolic health	
21. Associated factors of estimated desaturase activity in the EPIC-Potsdam study, Schiller et al., 2014.	NW OW	SCD16 Positive association.	<u>WHR</u> Positive association.
22. Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men, Warensjø et al., 2005.	NW OW	SCD16 <u>BMI</u> Significant positive association. <u>SCD18</u> Not significantly associated.	SCD16 <u>WC</u> Significant positive association, but possibly secondary to BMI. <u>SCD18</u> Not significantly associated.
23. Fatty acid composition and estimated desaturase activities are associated with obesity and lifestyle variables in men and women, Warensjø et al., 2006.	NW OW	SCD16 Significant positive association SCD18 No association	<u>WC</u> SCD16 Significant positive association (lost with adjustment for BMI). SCD18 No association. <u>VAT</u> SCD16 Significant positive association (lost among women with adjustment for BMI). SCD18 No association
24.	NW OW	SCD16	

Associations between estimated fatty acid desaturase activities in serum lipids and adipose tissue in humans: links to obesity and insulin resistance, Warensjø et al., 2009.		Significant positive association in serum PL SCD18 Significant negative association in serum PL	
25. Plasma stearoyl-CoA desaturase indices: Association with lifestyle, diet, and body composition, Vinknes et al., 2013.	OW OB	SCD16 Significant positive association SCD18 Significant positive association	<u>BF%</u> SCD16 Significant positive association SCD18 Significant positive association
26. Fatty Acid Profile and Desaturase Activities in 7–10-Year-Old Children Attending Primary School in Verona South District: Association between Palmitoleic Acid, SCD-16, Indices of Adiposity, and Blood Pressure, Bonafini et al., 2020.	NW OW OB	SCD16 Significant positive association SCD18 Negative association, but not significant	SCD16 <u>WtHR</u> Significant positive association (before adjustment for BMI) <u>FM</u> Significant positive association (before adjustment for BMI) <u>WtHR and FM</u> SCD18 Negative association, but not significant
27. Association between Serum Phospholipid Fatty Acid Levels and Adiposity among Lebanese Adults: A Cross-Sectional Study, Yammine et al., 2018,	NW OW OB	SCD16 Significant positive association among women (significance lost when tested for false discovery). SCD18 Significant negative association among women.	<u>WC</u> SCD16 Significant positive association among women (significance lost when tested for false discovery). <u>WC</u> SCD18 Significant negative association among women.
28.	NW	SCD16	

Fatty Acid Profile of Mature Red Blood Cell Membranes and Dietary Intake as a New Approach to Characterize Children with Overweight and Obesity, Jauregibeitia et al., 2020.	OW OB	Not significantly associated SCD18: Significant negative association.	
29. Visceral fat thickness in overweight men correlates with alterations in serum fatty acid composition, Kishino et al. 2008.	NW OW	SCD16 Significant positive association SCD18 Not significantly associated, but negative direction.	VAT SCD16 Significant positive association, but not independent of BMI. SCD18: Not significantly associated, but negative direction.
30. Relationship between the estimates of desaturase activities and cardiometabolic phenotypes in Koreans, Do, Chung, Moon & Shin, 2011.	NW OW	SCD16 Significant positive association SCD18 Not significantly associated, but negative direction.	WC SCD16 Not significantly associated, but positive direction. WC SCD18 Not significantly associated, but negative direction.
31. Serum Fatty Acids, Desaturase Activities and Abdominal Obesity – A Population-Based Study of 60-Year Old Men and Women, Alsharari et al., 2017.	OW	SCD16 BMI Not investigated.	SCD16 WC Significant positive association. WHR Significant positive association. VAT Significant positive association.
32.	NW OW SOB	SCD16 Not investigated.	SCD16 Liver fat Significant positive association.

Fatty acid metabolism is altered in non-alcoholic steatohepatitis independent of obesity, Walle et al., 2016.		Control study: Potential significant positive association.	Control study: Liver fat (ALT): Significant positive association.
33. Serum fatty acid composition and insulin resistance are independently associated with liver fat markers in elderly men, Petersson et al., 2010.	NW OW	SCD16 Not investigated.	SCD16 Liver fat (ALT): Significant positive association.
34. Palmitoleic acid is elevated in fatty liver disease and reflects hepatic lipogenesis, Lee et al., 2015.	OW OB	SCD16 Not investigated. SCD18 Not investigated.	SCD16 Liver fat Significant positive association. SCD18 Liver fat No association.
35. Fatty acid composition in serum cholesterol esters and phospholipids is linked to visceral and subcutaneous adipose tissue content in elderly individuals: a cross-sectional study, Rosqvist (2017)	NW OW	SCD16 BMI Potential positive association	SCD16 Abdominal SAT Significantly positively associated BF% Significantly positively associated VAT Not associated.
36. High Hepatic SCD1 Activity Is Associated with Low Liver Fat Content in Healthy Subjects under a Lipogenic Diet, Silbernagel (2012)	NW OW	SCD16 Not investigated.	SCD16 Liver fat Significant negative association
37. Low hepatic stearoyl-CoA desaturase 1 activity is associated with fatty liver and insulin resistance in obese humans, Stefan (2008)	NW OW OB SOB	SCD18 Not investigated.	SCD18 VAT Not associated BF Not associated

			Liver fat Significantly negatively associated, but association depended on BF%.

Abbreviations

Alanine aminotransferase (ALT), Body fat (BF), Body fat percentage (BF%), Body mass index (BMI), Cholesterol ester (CE), De novo lipogenesis (DNL), Fat mass (FM), Fat mass percentage (FM%), Normal weight (NW), Obese (OB), Overweight (OW), Phospholipids (PL), Percentage overweight (POW), Subcutaneous adipose tissue (SAT), Stearoyl-coenzyme A desaturase 1 (SCD-1), Stearoyl-coenzyme A desaturase 16 (SCD16 (enzyme activity estimated by finding the fatty acid ratio of palmitoleic acid (PAL) to palmitic acid (PA)), Stearoyl-coenzyme A desaturase 18 (SCD18 (enzyme activity estimated by finding the fatty acid ratio of oleic acid (OA) to stearic acid (SA)), Severely obese (SOB), Triglyceride (TGR), Visceral adipose tissue (VAT), Waist circumference (WC), Waist-to-hip ratio (WHR) and Waist-to-hight ratio (WtHR).

The association between estimated SCD-1 activity and BMI

All of the 37 studies in this literature review had used BMI to define overweight and obesity (except Abe et al. (2012) who used RW and Saito et al. (2014) who used POW). 32 studies had recruited OW participants, 18 studies had obese participants and three studies had severely obese participants (i.e., BMI above 40). In addition, 27 of the studies had included normal weight (NW) subjects for comparison or as a control group.

Four studies (Warensjø et al., 2009; Wolters et al., 2015; Svendsen et al., 2020 and Jauregibeitia et al., 2020) had used BMI as the only anthropometric and body fat indicator in their discussion of possible associations between hepatic SCD-1 activity estimates and excessive weight gain and body mass accumulation. The other studies had supplied the BMI index with data on additional AIs reflecting variations in body fat storage and/or distribution. However, 11 of the studies (Stefan et al., 2008; Paillard et al., 2008; Petersson et al., 2010; Silbernagel et al., 2012; Saito et al., 2014; Lee et al., 2015; Walle et al., 2016; Alsharari et al., 2017; Kang et al., 2017 and Lee et al., 2018) had used BMI mostly for recruitment purposes, and possible associations with BMI were not really investigated.

In 21 of the 23 articles that had investigated associations between SCD-1 and BMI as well as another AI, there were three articles in which they reported that associations with other indicators were dependent on BMI (Kishino et al., 2008; Do, Chung, Moon & Shin, 2011; Bonafini et al., 2018). In one study they had observed an association with another AI but not BMI (Hlavaty et al., 2015). Hlavaty et al. (2015) found that plasma PAL content was significantly associated with BMI and BF% and SCD16 activity was significantly associated with BF%, but they found no significant relationship between SCD16 estimates and BMI among the participating adolescents.

23 studies had chosen to estimate the SCD-1 enzyme's activity by calculating both the SCD16 index (the ratio of PAL to PA) and the SCD18 index (the ratio of OA to SA), while 12 had applied only the SCD16 index and two had applied only the SCD18 index. The choice of lipid fraction from which to calculate the SCD-1 estimates varied. Eight studies used total plasma (six) or serum (two) FAs, three studies used very-low-density lipoprotein triglycerides (VLDL-TGRs), one study used TGRs, nine used CEs and 16 used PLs. Three studies reported

significant associations when SCD-1 estimates were calculated based on data from only some of their applied lipid fractions (Steffen et al., 2008; Warensjø et al., 2009; Walle et al., 2016). A complete listing of lipid fraction specific associations is given in Table V in the enclosures section.

Among the studies that included obese participants, SCD16 and BMI were found to be convincingly associated in the study by Okada et al. (2005), Vinknes et al. (2013), Wolters et al. (2015), Aglago et al. (2014), Morcillo et al. (2017) and Bonafini et al. (2020) whereas equally convincing associations were found in an overweight population by Kishino et al. (2008), Saito et al. (2011), Do et al. (2011) Schiller et al. (2014) Del Pozo et al. (2020) as well as the three studies by Warensjø et al. (Warensjø, Risérus & Vessby, 2005; Warensjø et al., 2006 and Warensjø et al., 2009). Hlavaty et al. (2015), Abe et al. (2012), Rondanelli et al. (2015), Beccarelli et al. (2018), Svendsen et al. (2020) and Jauregibeitia et al. (2020) on the other hand, found no associations between SCD16 and obesity and Ojwang et al. (2020) found an inverse association. An additional eight articles found SCD16 and BMI to be less evidently (Steffen et al., 2008; Vessby et al., 2012; Choi et al., 2014; Yammine et al., 2018) or potentially associated (Paillard et al., 2008; Zeman et al, 2017; Rosqvist et al., 2017; Lee et al., 2018) (either because significance was lost with adjustment or when moving from baseline to follow-up or because the statistical analysis that had been included not was specific enough).

With regard to the SCD18 index, four studies (Saito et al., 2011; Vinknes et al., 2013; Rondanelli et al., 2015; Morcillo et al., 2017) found a significant positive association with BMI and eight found a significant negative association (Warensjø et al. 2009; Abe et al., 2012; Rondanelli et al., 2015; Aglago et al, 2017; Yammine et al., 2018; Jauregibeitia et al., 2020; Del Pozo et al., 2020; Ojwang et al., 2020).

The association between estimated SCD-1 activity and other anthropometric indicators

Rather than focusing only on associations between SCD-1 estimates and general body fatness as reflected by BMI, the majority of the articles had selected to deepen the analysis by also investigating excessive lipid storage in the abdominal area (abdominal subcutaneous and/or abdominal visceral fat) as well as liver fat.

Associations with increased FA accumulation in the abdominal area

The choice of body fat indicator(s) to fulfil the BMI index included WC (14), WtHR (4), WHR/SAD/VAT (8) as well as fat mass (FM)/fat mass percentage (FM%) (7) and android fat mass (1). The size of VAT and subcutaneous adipose tissue (SAT) had also been measured by CT or MRI. Liver fat (LF) was the focus in fives studies and was determined either isotopically, by performing biopsies or MR spectroscopy, or biochemically by measuring ALT.

10 studies reported a significant positive association between SCD16 and WC, four with WHR, two with WtHR and five with SAD or measured VAT. Three studies reported a significant positive association between SCD16 and BF%, while one study found a positive association with SCD18. Additionally, Okada et al. (2005), Vessby et al. (2012), Zeman et al. (2017) and Rosqvist et al. (2017) reported increased BF% in the highest BMI group, a group that also had significantly higher SCD16 indices than the low BMI group. Lee (2018) reported significant reductions in BF% concomitantly with significant reductions in SCD16 and BMI.

Regarding SCD18, one study found a significant negative association with WC, two found a significant negative association with WTHR while two studies rather observed a significant positive association between SCD18 and WTHR and two a significant positive between SCD 18 association and WC. Saito et al. (2014) found a U-shaped association between SCD18 and WHtR, it was inversely associated among the NW and positively associated among the obese (OB).

Lee et al. (2018) and Kang et al. (2017) had intentionally recruited participants with a similar BMI, because their intention was to investigate if they in an overweight (OW) state could observe possible associations between SCD-1 estimates and VAT independently of BMI. While Kang et al. (2017) found significant associations between SCD-1 estimates and VAT, this was not the case in the study by Lee et al. (2018). Also three other studies with OW participants in which they investigated the association between SCD16 and VAT however, they found positive association (Warensjø et al., 2006; Schiller et al., 2014; Alsararari et al., 2017), whereas Kishino et al. (2008) found a significant association, but it disappeared with adjustment for BMI. Rosqvist et al. (2017) reported that SCD16 was not associated with VAT, only with SAT.

Associations with increased FA accumulation in liver

Five of the included studies examined possible associations between SCD-1 and LF (Stefan et al., 2008; Petersson et al., 2010; Silbernagel et al., 2012; Lee et al, 2015; Walle, et al. 2016). Apart from the study by Stefan et al. (2008) and a reference study that had been included for comparison by Walle et al. (2016), they only focused on LF.

Stefan found a significant inverse relationship between SCD18 and LF, but this was only in the group with a high BF%. No associations between SCD18 and LF were observed in the lean group. Also Lee et al. (2015) investigated whether the SCD18 index was significantly related to LF possible, but found no associations.

Whereas Silbernagel et al. (2012) found a negative association between SCD16 and LF increase after a lipogenic diet invention, Petersson et al. (2010), Lee et al. (2015) and Walle et al. (2016), reported a significant positive association between SCD16 and LF independently of BMI. In the reference study included by Walle et al. (2016), they found a significant association with liver fat, but it disappeared with adjustment for BMI.

The possible influence of metabolic health upon observed associations between SCD-1 estimates and body mass and body fat distribution

Ten of the included studies (Warensjø, 2005; Kishino et al., 2008; Steffen et al., 2008; Do et al., 2011; Vessby et al., 2012; Choi et al., 2014; Rondanelli et al., 2015; Zeman et al., 2017; Svendsen et al., 2020; Ojwang et al., 2020) in their investigation of the SCD-1 enzyme's associations with excessive body mass and abnormal fat accumulation, had chosen to include a special focus on the enzyme's association with metabolic health indicators. Results were conflicting.

Warensjø et al. (2005) observed that SCD16 estimates were able to predict the metabolic syndrome, but according to their analysis the association was mainly explained by BMI. Kishino et al. (2008) on the other hand found that both NW and OW subjects defined as having and not having the metabolic syndrome did not have significant differences with regard to BMI, WC, VAT nor SCD16 and SCD18.

Steffen et al. (2008) observed that the significant association between SCD16 with BMI and WC lost significance in multiple regression analysis together with metabolic health indicators (associations with the AIs lost significance when metabolic health indicators were

considered). Likewise, Svendsen et al. (2020) found no associations whatsoever between SCD-1 activity estimates and BMI, but clear associations with metabolic health across all three BMI categories. Ojwang et al. (2020) in their study found associations between SCD-1 and both BMI and metabolic health, and this was both within and between BMI categories.

In the study by Rondanelli et al. (2015) and Lee et al. (2018) an intervention with energy reduction and dietary changes had been performed. At follow-up Lee et al. (2018) observed significant improvement in AIs and metabolic health indicators as well as reductions in SCD16. Correlation analysis between reduction in SCD16 and reduction in VAT was performed, but the association with SCD-1 did not reach significance. Likewise, Rondanelli et al. (2015) observed reductions in AIs and improved metabolic health after weight reduction and dietary changes. However, their population experienced no changes in neither SCD16 nor SCD18 estimates. Also Choi et al. (2014) observed associations with metabolic risk that were associated with BMI but independent of SCD-1.

23 studies included dietary data (Table 7). It did however vary the extent to which these data were actively used in the analysis. Five studies had conducted an intervention with positive dietary and lifestyle changes: Stefan et al. (2008), Wolters et al. (2015), Lee et al. (2018), Rondanelli et al. (2015) and Svendsen et al. (2020) (Svendsen et al.'s (2020) participants had undergone these changes in a previous study from which participants in the included study were recruited). In addition, Walle et al.'s (2016) participants as well as Morillo et al.'s study participants were on a standardised pre-surgery very low-calorie diet (VLCD). Silbernagel et al. (2012) conducted a clinical trial where an additional 600 kcal of monosaccharides was added to a balanced diet for 4 weeks and Lee et al. (2015) recorded detailed dietary information before a three-year long study on LF storage and associations with SCD-1 and DNL.

DISCUSSION

The association between estimated enzymatic SCD-1 activity and overweight or obesity as well as disproportionate and abnormal body fat accumulation.

The association between estimated SCD-1 activity and BMI

Even though BMI is the most widely used anthropometric indicator to estimate overall body fatness, it has its limitations and is more a measure of high weight than excess body fatness (Piqueras et al. (2021)). BMI does not address body composition nor fat distribution and may be misleading since an individual with high FM may have a lower BMI than someone with a large muscle mass, while someone with large fat depots in the abdominal area may still be NW. A person may be non-obese according to the BMI index, but obese by BF% (Vinknes, 2014, p. 13).

The morbidity rate associated with excess body weight varies between individuals of similar BMI and from different ethnicities (Piqueras, 2021). This may be related to genetic predispositions contributing to distinctive differences in body fat storage capacity and adipose tissue distribution (Rask-Andersen, 2019; Vinknes, 2014, p., 9, p. 14 and p. 48). These differences may translate into differences in associations between SCD-1 estimates and BMI.

In this literature review it was frequently observed and argued increased estimated hepatic SCD-1 activity (and especially increased SCD16) reflected that an elevated endogenous synthesis of MUFAs (and especially PAL) had taken place, and that this increased enzymatic activity was implicated in the occurrence of excess body mass and body fat accumulation. When total energy intake from the diet exceeds energy expenditure, the endogenous FA metabolism will be activated (Flowers & Ntambi (2009). This involves the synthesis, desaturation, and elongation of FAs. FAs and TGRs are synthesized in the liver before being transported to adipose tissue (Kishino et al., 2008). As such chronic overnutrition will result in increasing BMI.

In logistic regression Warensjø et al. (2005), Warensjø et al. (2006), Vinknes et al. (2013), Schiller et al. (2014), Wolters et al. (2015) and Bonafini et al. (2020), observed increased odds ratio (OR) for having a high BMI with increasing SCD16 activity estimates. Also Aglago et al. (2017), Morcillo et al. (2017), Yammine et al. (2018), and Del Pozo et al. (2020)

reported significant positive associations between SCD16 and BMI. As an example, Warensjø et al. (2006) observed that the risk of being OW increased with 50–60% for each SD increase in SCD16, and the predictive value remained after being controlled for physical activity and total fat intake (E%). Vinknes et al. (2013) observed that when moving from the 2.5 to the 97.5 percentile of estimated SCD16 there was a weight difference of 8 kg. while the weight increase for estimated SCD18 was 5 kg. These findings were significantly associated with both BMI and FM.

Just like SCD16, a high SCD18 activity was found to be associated with increased body mass (Saito et al., 2011; Vinknes et al., 2013; Morcillo et al., 2017). However, it was an inverse association with BMI that was most frequently reported (if at all estimated and associated). Among the NW, healthy participants included for comparison, it was most often observed that they had a combination of a low SCD16 and an equally high SCD18. In a normal physiology on an isoenergetic diet, a low SCD16 has been related to SFA oxidation and normal lipogenesis in the fed state while the inverse association between SCD18 and BMI has been related to a combination of sufficient levels of hepatic OA (either due to SCD18 activity or coming from the diet) and adipose tissue lipolysis (release of FFA) in the fasted state (Jaurgeibeita et al., 2020). Sufficiently high OA levels is essential for the preservation of cell function, insulin function as well as TGR synthesis for transport of excess lipids out of the liver to be re-esterified and stored in subcutaneous adipose tissue (SAT) (Stefan et al., 2008; García-Serrano et al., 2011; Silbernagel et al., 2012; Lee et al., 2015; Collins et al., 2017), something which will be returned to below.

Alternatively, a high SCD18 may reflect a large SAT and/or excessive adipose tissue lipogenesis and lipolysis of OA rich FAs entering the bloodstream in the fasted state (Hodson et al., 2008; Morcillo et al., 2017). In Vinknes et al.'s (2013) study SCD18 was significantly positively associated both with BMI and FM%. The high SCD18 index may have been related to that more than 70% of the study population was OW or obese as defined by BMI at the same times as their FM% was high. Kang et al. (2017) and Saito et al. (2014) however, observed that high SCD18 that was related to increased metabolic activity in the abdominal region. The SCD18 index may be confusing to interpret and is often found not to be associated body mass or body fat distribution. This may be related to the high availability of

OA in the diet, something which may dilute endogenous synthesis of OA by the SCD-1 enzyme. This issue will be returned to below.

Jauregibeitia et al. (2020) however, observed a decreased SCD18 index in the group with obesity compared to the children and adolescents with normal weight. This was due to lower levels of circulating OA and higher levels of SA. At the same time, the obese had an increased proportion of SFAs in their PL membranes. Jauregibeitia et al. (2020) argued that a shift in SCD-1 activity towards the PAL:PA pathway (as reflected by the SCD16 index) among the obese had left too little capacity of the enzyme for the OA:SA pathway represented by the SCD18 index. SCD-1 is supposed to protect against the harmful effects of SFA accumulation in tissues and bloodstream by metabolizing them into MUFA (Vessby et al., 2002; Silbernagel et al., 2012; Lee et al., 2015; Bonafini et al., 2018).

SA has been found to be the preferred substrate of SCD-1 (Peter et al., 2009). However, such a preference may possibly only be relevant with normalised values of PA and SA in the liver. In an environment with high values of SFAs (whether from the diet or the carbohydrate induced process of DNL) the desaturation of PA may take priority (researcher Fredric Rosqvist at the Department of Public Health and Caring Sciences, Clinical Nutrition and Metabolism, Uppsala University, personal communication, October 2021). This may be a physiological mechanism occurring in the body to protect itself from PA induced lipotoxicity (Vessby et al., 2002; Rosqvist et al., 2017; Bonafini et al., 2018; Collins et al., 2010).

Since all enzymes have a limited capacity (Hauge, Aakvaag & Christensen, 2001), the physiological need to avoid lipotoxicity may as such “exhaust” SCD-1 capacity (Collins et al., 2010; Silbernagel et al., 2012; Jaurgeibeita et al., 2022). PA that has been desaturated by SCD-1 into PAL may not be synthesised into OA (Figure 2)). The SCD18 index may become increased due to the elongation of PA into SA (Vessby et al., 2002; Warensjø et al., 2009) with the following SCD-1 synthesis of OA. If SCD16 is upregulated due to high PA however, this may result in a downregulated and insufficient SCD18 pathway. Then SA may become high. Lee et al. (2015) found that SA was positively associated with LF whereas Lee in the 2018 study found that weight reduction significantly decreased SA. These findings were attributed to increased SCD-1 capacity due to lower levels of PA. A sufficient OA content (either from the diet or endogenous hepatic synthesis) has been found to possibly be necessary to clear excess lipids and TGRs from the liver to be “safely” stored in SAT (Stefan

et al., 2008; Collins et al., 2010; Silbernagel et al., 2012; Rosqvist, 2017; Jauregibeitia et al., 2020). This may help to explain the often-observed negatively associated SCD18 index and positively associated SCD16 index observed in an overweight and obese state.

Stefan et al. (2008) observed that a low hepatic SCD18 in obese participants was associated with LF accrual whereas high SCD18 activity was associated with low LF content and high insulin sensitivity. Due to the essential role of OA in TGR synthesis and storage, they suggested that this indicated that high estimated SCD18 activity reflected high OA synthesis. This may have protected from palmitate-induced insulin resistance and lipotoxicity and fat accumulation in the liver by enabling TGR synthesis in the liver and export to SAT. Excess PA may result in lipotoxicity, something which may result in central obesity instead of expanding subcutaneous adipose tissue (which is better reflected by BMI) (Stefan et al., 2008; Collins et al., 2010; Silbernagel et al., 2012; Lee et al., 2015; Rosqvist et al., 2017).

Interestingly, Saito et al. (2011) found that while SCD16 was significantly positively associated with fasting insulin resistance and increased VLDL-TGR synthesis, the SCD18 activity ratio was only significantly positively associated with increased TGR synthesis. Furthermore, both SCD16 and SCD18 estimates were significantly positively associated with BMI, while SCD18 estimates as opposed to SCD16 were not associated with WHtR. This may perhaps illustrate that a high SCD18 ratio, indicating OA synthesis, enabled storage of FAs in SAT instead of in the trunk area.

A high BMI and total FM is not necessarily a bad thing. We are supposed to store excess energy in SAT (Slawik & Vidal-Puig, 2007); Tan, & Vidal-Puig, 2008; Fabbrini et al., 2009; Virtue & Vidal-Puig, 2010; García-Serrano et al., 2011; Ipsen et al., 2016). However, adipose tissue expandability and hence increasing BMI in response to positive energy balance is not an unlimited process. At some point a saturation point will be reached where SAT storage capacity has reached its limits (Slawik & Vidal-Puig (2007), Fabbrini et al, 2009; Tan & Vidal-Puig (2008); Virtue & Vidal-Puig (2010); Ipsen, Tveden-Nyborg & Lykkesfeldt, 2016; Longo et al, 2019). According to professor Kåre Birkeland, OW is often found to be compatible with metabolic health whereas there seems to be a breaking point when a person moves from the overweight category into obesity (Professor Kåre Birkeland, Faculty of Medicine, Institute for Clinical Medicine, University of Oslo, May 2021).

When SAT storage capacity has reached its limits, it becomes dysfunctional and characterised by insulin resistance and lipolysis. The surplus of FAs may instead become diverted to the abdominal area (Slawik & Vidal-Puig (2007). According to García-Serrano et al., 2011, it appears that in a positive energy balance, the amount of stored fat may be less important than the storage capacity of adipose tissue due to its effect on lipotoxicity, insulin resistance and propensity for storage of excess lipids in the abdominal area, both of which appear to affect SCD-1 activity and body fat storage.

It has been suggested that the metabolic effects of variations in SCD-1 activity become overt only under conditions with increased fatty acid flux to the liver due to metabolic dysregulation in adipose tissue (for example abnormal insulin function) or overfeeding (Silbernagel et al., 2012). In situations with an overflow of exogenous or de novo synthesized saturated fatty acids to the liver, insufficient increase of SCD-1 activity may result in hepatic accumulation of SFAs, liver damage and non-alcoholic fatty liver disease (NAFLD). According to Silbernagel et al. (2012) low SCD-1 activity aggravates SFA induced stress in the liver, inhibits the liver to secrete triglycerides and results in increased storage of LF. Efficient desaturation of SFAs into MUFAs by SCD-1 may instead preserve insulin function and hepatic capacity to clear triglycerides and prevent LF accumulation. Likewise, Lee et al. (2015) argued that the stimulation of the SCD-1 pathway in the liver during lipid overload due to systemic FFA delivery and hepatic DNL promoted the desaturation of SFAs by SCD-1 and protected adipose tissue against lipotoxicity and insulin dysfunction.

Insulin induces SCD-1, and insulin promotes both hepatic and adipose lipogenesis and FA accumulation (Otero et al., 2014; Lee et al. 2015; Smith et al., 2020). It is unclear however, how SCD-1 activity is affected by variations in insulin sensitivity and insulin concentrations (Vessby et al., 2002). Insulin resistance and/or high fasting insulin could result in excessive DNL and FA synthesis due to a failure to downregulate both hepatic and adipose tissue SCD-1 activity (Lee et al., 2015; Morcillo et al., 2017). Individuals with hepatic insulin-resistance have been found to have increased liver lipid synthesis, leading to hypertriglyceridemia (Santoleri & Titchenell, 2019). Theoretically however, abnormal insulin function could also downregulate SCD-1 activity and result in insufficient capacity to transform SFAs into MUFAs (and especially OA) and synthesise TGRs to be transported out of the liver and stored in SAT. Both processes could account for excessive adipose tissue lipolysis, a high delivery of FAs to

the liver and the accumulation of FAs in the liver or different adipose tissues. The effect of insulin dysfunction on SCD-1 regulation could also differ between the liver and adipose tissue (as well as different kinds of adipose tissue) (Vinknes, 2014; Lee et al., 2015; García-Serrano et al., 2011; Rosqvist et al., 2017).

Lipotoxicity and insulin resistance appear to be intimately and intricately associated with SCD-1 activity and body fat storage. Even though high hepatic SCD18 activity has been argued to be protective due to its enabling effect on subcutaneous adipose tissue lipogenesis and TGR synthesis and storage (Stefan et al., 2008; Silbernagel et al., 2012; Rosqvist et al., 2017; Jauregibeitia et al., 2022), high SCD18 estimates may also increase due to excessive lipogenesis and lipolysis in adipose tissue (Morcillo et al. 2017). In severe and long-term obesity, alterations may take place both in the liver and adipose tissue in the regulation of lipogenic transcription factors (like SREBP-1c) and lipogenic genes (like SCD-1) (Petersson et al., 2010; Saito et al., 2014; Morcillo et al., 2017). This may result in result excessive hepatic and adipose tissue lipogenesis and impaired fat oxidation (Warensjø et al., 2009; Petersson, 2010; Grønning-Wang, 2013; Vinknes, 2014, p. 46; Morcillo, 2017; Olga et al., 2020; Iizuka et al., 2020).

Numerous nutritional and environmental factors can induce epigenetic modifications (changes in the expression of the genetic code) that influence transcriptional factors, genes and obesity (Morcillo et al., 2017; Olga). The aim of Morcillo et al.'s (2017) study was to evaluate whether adipose tissue SCD mRNA expression and the methylation SCD gene promoter was associated with the metabolic improvement in morbidly obese patients after bariatric surgery. The procedure resulted in dramatic metabolic improvement, reduced BMI and WC, significantly decreased hepatic SCD-1 estimates, improved insulin function and reduced lipolysis. The changes occurred simultaneously with downregulation of SCD m-RNA expression and increase in the low SCD promoter methylation. DNA methylation typically acts to repress gene transcription ("transcriptional silencing") (Morcillo et al., 2017, p. 5).

Interestingly, Morcillo et al. (2017) observed significantly decreased SCD16 and SCD18 enzymatic activity and downregulation of SCD m-RNA expression and increased SCD-1 methylation promoter only among the participants who lost the most weight (above the 75th percentile). This may potentially indicate that in the severely obese segment large reductions in adipose tissue may be needed before genetic and epigenetic alterations

reducing the expression of lipogenic genes and SCD-1 activity may be observed, as well as improved insulin function and reduced lipogenesis.

This interpretation is made more probable by the fact that serum SCD-1 indices were not associated with the significant increase in SCD-1 methylation promoter and SCD gene expression, only with the reduction in lipolysis and insulin resistance. As such it seems like it was the reduction in lipolysis and insulin resistance rather that the reduction in BMI and/or WC that had decreased hepatic SCD-1 activity. Furthermore, even though SCD-1 activity was not significantly reduced, also the participants who lost less weight experienced significantly improved metabolic health (although at a lower scale). Taken together, this may perhaps indicate that the metabolic alterations came before reductions in SCD-1 estimates, but that both the metabolic improvement and reduced SCD-1 activity were related to body mass/WC reduction, i.e., that it was the loss of body fat that was the actual initiating factor.

High SCD16 and SCD18 indices, was in this literature review found to not only occur in a severely obese state nor to only be associated with general fat accumulation. Likewise, despite chronic overeating that over time results in overweight and obesity, SCD-1 activity estimates may remain on a moderate level and/or remain similar to individuals with a normal BMI. This was exemplified in the studies by Rondanelli et al. (2015), Beccarelli et al. (2018), Ojwang et al. (2020) and Svendsen et al. (2020). The studies by Lee et al. (2015), Walle et al. (2016) and Kang et al. (2017) illustrated that significant differences in BMI are not a necessary criterium for observing significant variations in estimated SCD-1 activity.

The association between estimated SCD-1 activity and abdominal obesity

Judging from the observations reported in this literature study, it appears to be necessary to investigate associations with SCD-1 estimates in an overweight and obese state with additional anthropometric and metabolic health indicators (MHIs) to assess possible associations between estimated SCD-1 activity and overweight and obesity. Of the studies that found a significant association between SCD-1 and BMI, as many as 17 studies had performed statistical analysis that uncovered a significant association also with an AI reflecting excessive lipid accumulation in the trunk area. As such, also AIs reflecting excessive and abnormal body fat accumulation in the abdominal area need to be discussed.

The physiological mechanisms behind the activation of the SCD-1 enzyme in a metabolic state characterised by central obesity and other metabolic syndrome related traits may be different from the mechanisms behind overall overweight or obesity. While BMI has been argued to indicate overall excessive body fat accumulation, AIs like WC, WHR and LF have been proposed as indicators of compromised metabolic health resulting in dysfunctional and abnormal fat accumulation in the trunk area. At the same time however, BMI and ectopic fat deposition may be interlinked and help elucidate each other.

Guh et al. (2009) argued that due to the health consequences of having a disproportionate body fat distribution, excess android fat mass should be diagnosed as OW even if BMI is within the normal range. Likewise, Araújo et al. (2019) argued that WC, and especially VAT, could be considered surrogate markers for someone's metabolic health. Even though it is often argued that it is mostly obesity that is related to health problems (WHO, 2022; Nuttall, 2015), it has been established that the risk of serious disease may escalate already when someone is slightly OW (Field et al., 2001; Guh et al., 2009; Aune et al., 2016). In their meta-analysis, Aune et al. (2016) found that the optimal BMI was as low as 20-22 in the healthiest segment. Likewise, even small differences in BMI have been found to possibly have an influence on all-cause mortality (Aune et al., 2016 and Global BMI Mortality Collaboration, 2016). This may be related to the findings documented by Kang et al. (2017). in their OW population with similar BMI, they observed significantly higher estimated SCD-1 activity among the subjects with the largest amounts of VAT.

Saito et al. (2014) discussed these associations in an obese population with abdominal obesity (subcutaneous and visceral abdominal fat had not been differentiated), and they investigated only SCD18 estimates. It was suggested that SCD18 regulation was associated with abdominal fat as well as being related to leptin and insulin function. Saito et al. (2014) found that SCD18 activity estimates had a U-shaped relationship with WHtR. SCD18 was inversely associated with WHtR among children without abdominal obesity, but positively with WHtR among children with abdominal obesity. As opposed to the children without abdominal obesity however, the children with excessive abdominal tissue also had high SCD18 and high leptin levels.

Saito argued that the U-shaped association was related to impaired leptin function among the children with abdominal obesity. Leptin is supposed to suppress SCD-1 activity

independently of insulin. As such, leptin resistance could have contributed to excessive hepatic lipogenesis due to the failure of leptin to suppress SCD-1 activity. Since also insulin resistance may upregulate FA synthesis in the liver (Santoleri & Titchenell, 2019), the combination of leptin and insulin resistance could have resulted in a significantly increased lipid load. FAs from enhanced lipogenesis and MUFA synthesis in the liver may have become diverted to the abdominal area due to an inability to store it all in SAT. The children with abdominal obesity however, also had significantly higher percentage overweight (POW) than the children without abdominal obesity. Whether SCD18 was associated with POW at the time of FA measurement is unknown. POW may have developed before abdominal obesity started to appear. Importantly, the effect of leptin may indirectly have influenced SCD-1 activity and fat gain due to its role in regulating satiety levels, i.e., the suppression of hunger and termination of eating.

Like Morcillo et al. (2017), Saito et al. (2014) suggested that increased abdominal obesity was associated with altered expression of lipogenic transcription factors and genes that may have disrupted the ability of leptin to suppress SCD-1 and terminate lipogenesis. As such a combination of leptin and insulin resistance may have failed to down regulate FAs synthesis as well as decrease the ability to synthesise TGR to be stored in SAT (perhaps in combination with insulin resistance and lipolysis), further contributing to the development of abdominal obesity and deteriorating body fat distribution. Saito et al. (2014) could not investigate the effect of insulin upon SCD18 regulation and FA storage in their population due to the lack of data.

The influence of leptin on SCD-1 regulation, was also discussed in the study by Okada et al. (2005). As opposed to Saito et al. (2014), Okada et al. (2005) studied the SCD16 index, and found that it was positively associated with leptin. Like Saito et al. (2014), they suggested that an insufficient suppression of SCD16 activity by leptin contributed to increased endogenous lipogenesis and MUFA synthesis in the liver. They also observed that SCD16 was significantly positively associated with abdominal obesity, and especially visceral tissue. In multiple regression analysis however, they discovered that the association with leptin lost significance. Interestingly, also FM% lost significance with further testing. This may have reflected the mentioned redirection of excess lipids to the trunk area rather than SAT. The obese children also had significantly higher BMI as well as significantly higher SCD16 and

leptin, but SCD16 did not appear to be associated with BMI. A correlation analysis was only performed between SCD16 and PAL, but PAL is normally considered to provide a fairly accurate reflection of SCD16 activity (Okada et al., 2005, Chong et al., 2008; Lee et al., 2015; Rosqvist et al., 2017; Walle et al., 2016; Rosqvist et al., 2022). PAL was significantly associated with WHR, but not with BMI.

As mentioned, BMI and ectopic fat accumulation may be interrelated. Kishino et al. (2008) argued that obesity, and particularly abdominal obesity, resulted from an increase in visceral fat. They had recruited a population in which there were both NW and OW participants with metabolic syndrome related traits. However, the association between SCD16 and VAT was found to be dependent on BMI. SCD16 was only significantly associated with VAT among the OW participants. Also Bonafini et al. (2020) observed that AIs of central obesity were dependent on BMI, while Do et al. (2011) found significant associations with BMI, but not WC.

Kang et al. (2017) however, compared within and not between BMI categories. They intentionally wished to study the effect of VAT and as such recruited individuals that matched each other with respect to BMI but differed in the size of their VAT. They had divided the participants into three groups with significantly increasing VAT and observed that participants with a large VAT also had higher activity of SCD16 and SCD18 than OW participants with less visceral fat. The significant differences in SCD-1 activity estimates were retained after adjustment for BMI. The effect of adding BMI among the adjustment factors however was the opposite for SCD16 and SCD18 respectively. Whereas the significance was somewhat weakened for SCD16 (and as such may indicate a potential influence of BMI upon results), it was slightly increased for SCD18. This could potentially indicate a stronger association with VAT. Had the VAT groups differed more in BMI, a possible influence upon SCD-1 indices that also was related to BMI may possibly have become apparent. Kang et al. (2017) concluded however, that the distribution of body fat significantly affects FA composition and SCD-1 activity not only in obese subjects, but also in OW status.

As exemplified above, excessive fat accumulation in the abdominal region has been related to elevated SCD18 activity (Saito et al., 2014; Kang et al., 2017; Del Pozo et al., 2020). In this literature review however, the SCD18 index was mostly found not to be associated with abdominal obesity (Okada et al., 2005; Warensjø et al., 2006; Stefan et al., 2008; Choi et al.,

2014; Lee et al., 2018) whereas it was found to be negatively associated among women in a couple of the studies (Agalgo et al., 2017; Yammine et al., 2018). As a reflection of endogenous FA synthesis, it was especially increased SCD16 activity that was found to be significantly positively associated with abdominal obesity (Okada et al., 2005; Warensjø et al., 2006; Saito et al., 2011; Schiller et al., 2014; Alsharari et al., 2017; Aglago et al., 2017; Yammine et al., 2018).

Subcutaneous adipose tissue (SAT) can expand and remodel to adapt to changes in energy supply and energy requirements (Ipsen et al., 2016). As mentioned however, there is a limit to how much fat it may store. When it has reached its limits, it becomes dysfunctional and unable to store excess lipids. The surplus of FAs will be diverted to the abdominal area (Slawik & Vidal-Puig (2007). According to Ipsen et al. (2016) however, chronic over-nutrition may result in SAT dysfunction already before SAT has reached its limits. SAT dysfunction results in ectopic deposition of excess lipids due to an inability to store the surplus in SAT. Compared to SAT, abdominal adipose tissue, and especially VAT, has been found to be highly metabolically active even in the fasted state due to a combination of insulin resistance and lipolysis. The end result is systemic metabolic impairment characterised by lipotoxicity and inflammation.

Rosqvist et al., 2017 argued that the relative accumulation of abdominal visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (SAT) is of greater importance than the total amount of SAT. It is especially abdominal VAT that has been argued to be responsible for the many metabolic abnormalities associated with abdominal obesity, and a reduction in visceral fat has become a key therapeutic goal in the management of obesity (Fabbrini et al., 2009; Petrus et al., 2017). Compared to VAT, abdominal SAT has been argued to be less insulin resistant and lipolytic (Porter et al., 2009; Kang et al. 2017; Rosqvist et al, 2017). It has even been demonstrated that abdominal SAT may be protective among subjects with a large VAT (Porter et a., 2009). In many of the included articles it was stressed that visceral obesity causes several metabolic dysregulations including an altered lipid profile and increased SCD-1 activity (Kishino et al., 2008; Rosqvist et al., 2017; Kang et al., 2017; Lee 2018).

Rosqvist et al. (2017) investigated the association between estimated SCD16 activity and the size of abdominal SAT and VAT respectively in a population of OW elderly men and women.

It was discovered that serum SCD16 was significantly positively associated with the size of SAT and FM%, but not VAT. Both insulin resistance and serum PA however were significantly positively associated with the size of VAT. Rosqvist et al. (2017) suggested that the concomitant existence of insulin resistance and a large VAT may indicate inadequate ability to store excess energy in abdominal SAT. Among participants with large VAT area, a combination of, increased hepatic lipogenesis and/or high dietary SFAs as well as adipose tissue insulin resistance and lipolysis may have overloaded the liver with FAs and exhausted SCD-1 capacity (Silbernagel et al., 2012; García-Serrano et al., 2011). Insufficient desaturation of PA and synthesis of OA may have added to the problem to ensure hepatic TGR synthesis and storage of excess energy in SAT and/or abdominal SAT (Stefan, 2008). This would instead contribute to storage of excess LF (Silbernagel et al., 2012; Lee et al., 2015).

Interestingly, the children with abdominal obesity and high SCD18 in Saito et. al.'s study, had both significantly higher WHtR as well as significantly higher POW (BMI). Since WHtR is a reflection of central obesity and not VAT, the high SCD18 observed by Saito et al. (2014) may have reflected increased abdominal SAT rather than increased abdominal VAT. Likewise, Del Pozo et al. (2020) observed that SCD 18 was significantly positively associated with WC, but not WHR (which is a reflection of VAT).

As opposed to what Rosqvist et al. (2017) found regarding the association between hepatic SCD-1 activity estimates and the size of VAT and SAT respectively, Petrus et al. (2017) observed the opposite relationship in the actual FA composition of the two adipose tissues. Judging from the FA composition of VAT, SCD-1 activity was higher in abdominal VAT than in abdominal SAT. This was possibly related to a high release of PA from the liver to the circulating bloodstream had been delivered to VAT, and therefore had activated adipose tissue SCD-1 activity. Compared to abdominal SAT, SCD gene expression was also higher in abdominal VAT, and was associated with a FA profile characterised by a high proportion of SFAs. Taken together, the observations made by Petrus et al. (2017) may have been related to the metabolic activity of VAT, reflecting the combination of lipogenesis and lipolysis, and helps to understand the observations made by Rosqvist et al. (2017) regarding an association between serum SCD16 activity and the size of abdominal SAT and abdominal VAT respectively. A sufficient SCD16 activity was associated with FA storage in abdominal SAT instead of abdominal VAT.

Also García-Serrano et al. (2011) in their severely obese population observed that SCD-1 activity was differently regulated in abdominal VAT and abdominal SAT. They argued that the activity in adipose tissue was related to hepatic SCD-1 activity and MUFA synthesis. High SCD-1 activity in VAT was associated with insulin resistance, whereas high SCD-1 in SAT was associated with BMI. García-Serrano et al. (2011) suggested that the high level of SCD-1 activity among the subjects with a healthy insulin function favoured the storage of fat in SAT instead of the metabolically detrimental VAT. It was argued that their findings were equally relevant for the regulation of hepatic SCD-1 activity and insulin function.

Rosqvist argued that reduction of VAT and liver fat was primarily depended on improved insulin function, and only secondary associated with hepatic SCD-1 regulation (Rosqvist et al., 2017; Rosqvist et al., 2019a; Rosqvist et al., 2019b).

Lee et al. (2018) had introduced an intervention consisting of reduced energy intake and changes in dietary composition. The treatment group between baseline and follow-up experienced significant reductions in BMI, WC, VAT, FM% and total FM as well as significantly improved insulin sensitivity. Likewise, SCD16 activity estimates and levels of circulating PA, PAL, SA and OA were significantly reduced, indicating reduced DNL and MUFA synthesis. Due to the significant reduction in SCD-1 related FAs it could have been expected that SCD-1 activity estimates would be significantly associated with VAT reduction. In correlation analysis however, it was discovered that SCD16 was not significantly associated with the reduction in VAT. This may have been due to a continued need for reduction in insulin resistance and reduction in VAT before significant associations between reductions in SCD16 and VAT could be observed.

Interestingly, Kang et al. (2017) found that a certain size of VAT was necessary before significant associations between estimated SCD-1 activity and the size of VAT were observed. This may be related to why Lee (2018) despite significant reductions in BMI and VAT saw no significant associations between SCD-1 indices and VAT. Also Kishino et al. (2008)found significant correlations between SCD16 indices levels and VAT among the OW, but not the NW. These observations may be related to the findings made by Morcillo et al. (2017) i.e., that genetic changes in the SCD-1 promoter seemed to require a certain degree of body mass loss. As discussed, Petrus et al. (2017) found increased SCD gene expression in adipose VAT.

Paillard et al. (2008) investigated associations between SCD16 and abdominal adiposity in a male only population. The high circulating PA and PAL content indicated increased hepatic lipogenesis and increased SCD16 activity (SCD18 was not associated). The subjects with high SCD16 activity also had increased hepatic TGR secretion as well as increased FA accumulation in the abdominal area. In correlation analysis Paillard et al. (2008) divided the participants into a high and a low TGR group and investigated measured PAL as an expression of SCD16 activity. They concluded that it was high TGR rather than high PAL that was most strongly associated with high WC. Interestingly however, before TGRs were added to the model it was PAL that was most strongly associated with WC whereas when TGR was added to the model it was age (and neither TGR nor PAL) that was most strongly associated. Accordingly, since PAL was more strongly associated with WC than age before circulating TGRs was included as an independent variable, PAL may actually have had a stronger independent association with WC than TGRs. The association between TAG and WC may have been confounded by age.

The mean age of the participants in Paillard et al.'s study (2008) was 41 (although the age range was very wide). Both among men and women, TGR levels and WC increase with age (Kreisberg & Kasim, 1987; Stevens, Katz & Huxley, 2010). Among women TGR increase steadily whereas they among men reach a maximum between 40 and 50 years of age (Kreisberg & Kasim, 1987). In both genders, abdominal SAT and abdominal VAT increase with aging. According to Stevens et al. (2010) "A large portion of this increase is driven by gains in body weight, but the increases observed are larger than those would be predicted from increases in BMI alone, and increases in WC are seen with aging in the absence of weight gain" (p. 11).

The study by Morcillo et al. (2017) exemplified the possible association between genetic alterations and changes in hormonal and/or other metabolic functions, as well as associations with elevated SCD-1 activity and excess body mass and body fat. Genetic factors are considered to explain 40–70% of body weight and body composition (Vinknes, 2014, p. 48). It has been argued that the capacity for SAT storage and hence the degree of excess body fat that is compatible with metabolic health is genetically regulated and may vary from person to person (Tan & Vidal-Puig (2008)). Inter-individual differences in response to FA

overload may affect metabolic processes in which SCD-1 activity is closely involved (Hodson, Rosqvist & Parry, 2020).

On a general basis however, women seem to have the ability to store more fat in SAT (especially until the end of menopause). Warensjø et al. (2006) argued that women's higher SCD-1 activity estimates may be associated with a genetic predisposition for having an increased FM, perhaps due to women's role in childbearing (Warensjø et al., 2006). Men accumulate comparatively more fat in the abdominal region (Warensjø et al., 2006; Stevens et al., 2010). As such, it may be speculated if BMI is more representative for observations on associations between SCD-1 estimates and BMI among women than men.

In their borderline OW population, Warensjø et al. (2006) found that SCD16 was more strongly associated with BMI among women than men. In bivariate analysis in the total population SCD16 was significantly positively associated with BMI, WC and SAD (VAT). When BMI was adjusted for however, the association with VAT disappeared (ie they found no significant association between SCD16 and VAT independently of BMI). When the analysis was broken down according to gender however, VAT remained significantly associated among men also after adjustment for BMI. Whereas SCD16 was most closely associated with increased BMI among women, it appeared to be relatively more closely associated with VAT among men. Warensjø et al. (2016) argued that the closer association with VAT than BMI observed among men, was related to that SCD16 activity had been increased due to central adiposity whereas estimates among women were more related to general overweight. They suggested that this was related to women's increased capacity for SAT storage.

Alsahariri et al. (2017) made interesting observations in both domains. Their population was in their 60s. Irrespectively of gender, they found that OR for observing abdominal obesity (increasing WC, WHR and SAD (VAT)) was significantly increased with increasing proportions of measured serum estimated SCD16 activity. Interestingly, Alsharari et al. (2017) observed that compared to men, women had significantly lower serum PA, but a higher SCD16 index. However, women also had lower fasting insulin.

Since BMI cannot directly reflect the relative proportion of adipose versus lean tissue nor body fat distribution and FM% (Vinknes, 2014, pp. 10 - 11; Piqueras et al., 2021), findings in associations between SCD-1 indices and BMI may be affected by gender and age. In the

elderly, there is a redistribution of body fat to the abdominal region and as such BMI may become less reliable in the elderly population (Piqueras et al., 2021). Likewise, after menopause, differences in body fat accumulation also become more similar between the genders.

Alsharari et al. (2020) suggested that dissimilarities in associations between men and women may have been related to gender differences in fat accumulation and hormone-dependent differences in lipid metabolism that were still relevant even though they had reached their 60s. However, Alsharari et al. (2020) also stressed the possible influence of dietary and lifestyle factors. Since women had significantly lower serum PA, but a higher SCD16 index as well as lower fasting insulin, this may once more demonstrate the necessary and beneficial metabolic activity of the SCD-1 enzyme. Even though its elevation may be a sign of metabolic stress, this may not be the case in a context of metabolic homeostasis were PA induced lipotoxicity is avoided by ensuring sufficient clearance of FAs from the liver, storage in SAT and avoidance of excessive lipolysis. Alsahariri et al. (2017) concluded that diets high in SFAs, and in particular PA, may promote the development of abdominal obesity and the metabolic dysregulation (including insulin resistance) since it will put stress on the SCD-1 enzyme, diverting capacity towards the PAL:PA pathway away from the OA:SA pathway.

In Vinknes et al.'s (2013) population-based study among subjects in their 70s, they had supplied the analysis of associations between SCD16 and SCD18 estimates and BMI with associations between SCD16 and SCD18 and total FM adjusted for lean body mass. They found the same significant associations with SCD-1 enzymatic activity with total FM as they had found for BMI. No gender related differences became apparent when Vinknes applied BMI and FM. Unfortunately, it was not possible to investigate associations between SCD-1 and central obesity in this study since no AI reflecting body fat distribution was included.

The issue of abdominal obesity appears to be relevant also in a young population. Gender differences in FA storage and capacity begin early in life and become more apparent in puberty due to changes in sex hormone levels Kelsey, M. M., & Zeitler, P. S. (2016). In this literature review all the included articles conducted in a population of children and/or adolescents found associations between SCD16 and increased body mass and/or abdominal fat and metabolic risk, with the only exceptions being Beccarelli et al. (2018) and Abe et al. (2012). Abdominal obesity has been found to be partly hereditary; genetic variations in the

SCD gene that have been associated with body fat distribution and insulin sensitivity have been observed (Warensjø et al., 2007). As many as five of the studies among children had been conducted in Korea and Japan, a part of the world where abdominal obesity and the metabolic syndrome has increased disproportionately compared to the rest of the world (Rampal et al., 2012).

Olga et al. (2021) investigated lipid markers and SCD16 activity in children from infancy until their early 20s. They reported that children who had gained excessive weight-for-length during the first 3 months postnatally were also to an increasingly extent found to have higher weight, BF% and increased metabolic risk at age 21. To explain these findings, they argued that variations in weight and propensity for weight gain not only could be attributed to the imbalance between energy consumption and energy expenditure, but variations in FAs and SCD-1 regulated processes that become established already in infancy. By referring to studies with adult participants that have found strong associations between the activity of SCD-1 and the FA composition in diet, they emphasised that variations in diet already in early life possibly could influence FA composition the effects of and enzymatic activity, and as such on growth and metabolism. They demonstrated that could be associated with subsequent weight gain. Furthermore, they stressed that dietary FAs have been found to be able to modulate desaturase activity not only in the short term but to possibly also in the long term due to their influence on epigenetic changes.

The association between estimated SCD-1 activity and liver fat

Excessive lipogenesis and lipolysis are two processes that may flood the liver with FAs and result in accumulation of LF (Lee et al., 2015; Ipsen et al., 2016; Rosqvist et al., 2019a). Both overweight and obesity have been associated with liver fat build up (Petersson et al., 2010; Walle et al., 2016).

Stefan et al. (2008) observed that insufficient SCD18 activity in the liver seemed to reduce the capacity of the liver to clear intrahepatic TGRs in VLDL. They suggested that high SCD18 may protect against LF build-up. Since the association with LF depended upon the participants BF%, Stefan concluded that hepatic SCD18 activity may protect from LF accumulation among the obese.

Likewise, it appears to be no necessary relationship between increased SCD16 and increased LF. Silbernagel et al. (2012) in their OW population found that a high SCD16 index was negatively associated with LF. Four weeks on a lipogenic (i.e., excess energy) diet consisting of monosaccharides resulted in a body weight increase of 1.2% and increase in liver fat by 33%. Estimated SCD16 however, was negatively associated with the increase in liver fat.

Both in Lee et al.'s (2015) obese and Walle et al.'s (2016) severely obese population they had included a participant group with normal livers in addition to the participants with high liver fat. In both studies they observed that despite similar BMI between the liver fat groups, the high liver fat group had significantly higher SCD16 activity. Likewise, Rosqvist et al. (2014) conducted an intervention trial with only NW healthy participants. They found a significant positive association between SCD16 and LF and concluded that "Hepatic activity of the lipogenic enzyme SCD-1 may be elevated in steatosis" (p. 2361). As such the study exemplifies that both high SCD16 and LF accumulation is not limited to overweight and obesity.

Also Petersson et al. (2010) investigated whether LF varied despite similar BMI. However, the SD for BMI was large enough to potentially have uncovered an association. When they adjusted the association between SCD16 and LF for BMI however, the positive relationship between SCD16 and LF remained virtually unaffected. The significant independent relationship between SCD16 and liver fat (measured by ALT) also remained after being controlled for WC and insulin resistance. Like Lee et al. (2015) and Walle et al. (2016), Petersson et al. (2010) concluded that estimated SCD16 activity and was primarily associated with LF.

However, Walle et al.'s (2016) severely obese subjects had similar BMI, but both the medium and high LF group had significantly higher SCD16 activity than the group with normal LF. The significance of the association with LF was increased after adjusting for among other BMI, gender, fasting insulin and the presence of diabetes. Even though there were no significant differences in BMI when comparing the high and the middle LF group, an effect of BMI on LF cannot be ruled out. There was a steadily increasing BMI when moving from normal LF to medium to high LF. Furthermore, since BMI was only one of several adjustment factors, the contribution of BMI in the equation is unknown. In addition, it is not possible to disregard the possibility of residual confounding. The spread of data around the mean of BMI was also

high. As such, it cannot be excluded that BMI potentially may have had an influence on the observed associations between SCD16 and LF. In addition, there may have been associations with AIs reflecting body fat distribution (for example VAT).

To investigate the relevance of the findings among severely obese bariatric patients on a VLCD diet, Walle et al. (2016) compared their observations with data from a population-based study. In this moderately OW population, SCD-1 had been found to be significantly positively associated with LF (measured as ALT). However, the high LF group also had significantly higher BMI, and adjusting for confounding factors uncovered that associations between SCD16 and LF were dependent on BMI. DNL was also significantly positively associated with LF, but again the association was dependent on BMI.

Taken together however, there seems to be fairly strong indications of a relationship between SCD-1 activity and excessive LF accumulation that is at least partly independent of overweight and obesity. This is perhaps not surprising considering the enzyme's multifaceted function in lipid metabolism and high expression in the liver (Frayn, 2010, p. 92; Vinknes, 2014, p. 18; Alves-Bezerra & Cohen, 2017).

The association between estimated SCD-1 activity and metabolic health

So far it has been uncovered that both total fat mass and evenly distributed SAT as well as disproportionate body fat distribution and liver fat should to be taken into consideration in order to elucidate associations between estimated SCD-1 activity and overweight and obesity. Even though both body fatness and abnormal lipid accumulation are taken into consideration however, it still seems to be necessary to investigate additional variables. Variables that have been mentioned are insulin and leptin regulation a well as variations in FFAs and triglycerides. Judging from what has been revealed so far, it appears necessary to investigate possible systematic associations between SCD-1 estimates and metabolic health.

Possible associations with metabolic health could explain why it sometimes is difficult to interpret SCD-1 estimates. Since the SCD-1 enzyme is closely involved in lipid metabolism, SCD-1 activity estimates may look similar when estimated from the circulating FA composition, even though they reflect different physiological mechanisms and interconnections. This adds to the importance of considering additional variables when interpreting associations between SCD-1 estimates and overweight and obesity. As an

example Saito et al.'s study (2014) could be mentioned. Among the participants without abdominal obesity, the high SCD18 activity may have been related to normal FA metabolism in the fasted state (as explained above) whereas it among the participants in the abdominal obesity group may have been related to excessive hepatic lipogenesis as well as metabolic dysfunctions resulting in abdominal obesity, insulin resistance and lipolysis.

Also SCD16 estimates may be confusing. Vessby et al. (2012) demonstrated that this index may become highly elevated in a normal physiology, and comparatively lower among the participants that are more OW. Vessby et al. (2012) observed that even dramatically increased SCD16 estimates and circulating PAL may not necessarily be associated with a high BMI. In their study they investigated two groups of women, one living in a traditional hunter-gatherer community and one group of women living in Lima. Despite having significantly higher levels of PAL, OA and SCD16 activity estimates (and probably SCD18, but this ratio had not been calculated), they had lower BMI and BF% compared to the women from Lima. They also had perfect metabolic health. Vessby et al. (2012) argued that the high proportions of PAL and OA in the plasma lipids of the women from the Shuar region reflected adipose tissue – and not hepatic - lipogenesis and subsequent SCD-1 desaturase activity, and as such that the high proportion of MUFAs in the bloodstream reflected normal adipose tissue lipolysis in the fasted state. In the study by Vessby et al. (2012), it was illustrated how SCD-1 operates in a metabolically healthy physiology; feeding increased insulin production and in the normal state this will also upregulate SCD-1 and they work in concert to clear the lipid load from the blood stream to be stored in AT. In the fasted state, FAs were released to the blood circulation to provide energy. In a state of insulin resistance however, SCD-1 activity estimates may reflect altered FA metabolism, among other due to high SFA load and lipotoxicity.

It needs to be remembered however that two factors may be related long before they produce observable manifest symptoms. Beccarelli et al. (2018) focused on the possibility of a connection between insulin resistance, hepatic SCD-1 activity, and adiposity. Even though they found no significant differences in FA composition and SCD-1 enzyme activity among the children based upon their BMI classification, they found significantly compromised insulin function among the OW and OB children compared to the NW. SCD16 and SCD18 were significantly positively associated with fasting insulin and SCD16 was also significantly

positively associated with insulin resistance (HOMA-IR). This is interesting since insulin resistance has been argued to be especially relevant for hepatic insulin regulation whereas fasting insulin levels have been more associated with insulin function in SAT (Lee et al., 2015).

Beccarelli et al. (2018) suggested that "…while there are physical changes occurring as children's BMI moves up, they may not yet be experiencing aberrations in lipid metabolism" (p.48). They stressed that since insulin has been observed to induce SCD-1 activity, their findings may be an illustration of such a regulatory role of insulin upon SCD-1 enzymatic activity. They indicated that SCD-1 activity could become upregulated with further increases in BMI. Beccarelli et al.'s (2018) explanation to the lack of significant differences in SCD-1 estimates between the various BMI categories, could be an illustration of how the body despite metabolic stress to a certain extent is able to adjust to remain healthy.

In Beccarelli et al.'s (2018) population however, insulin abnormality was not associated with excessive FA accumulation in the abdominal area. Interestingly, the children in the OW category had a lower WC and WHR than the NW while the obese had the highest measures. Likewise, the OW had considerably lower levels of circulating SFAs than both the NW and obese as well as higher levels of MUFAs. Again it was the obese that had the highest level of SFAs. This may possibly illustrate an association between SFAs and ectopic FA storage (this will be returned to below). Whether the excess FAs among the NW and obese were related to dietary SFA or DNL due to carbohydrate is unknown. however, SCD-1 activity in the three BMI categories may potentially have become highly affected by dietary differences.

As opposed to Beccarelli et al. (2018), Choi et al. (2014) observed that SCD-1 indices were positively associated with BMI already in OW status whereas an association between insulin and metabolic health only became apparent among the obese. Choi observed that the OW and obese boys had identical SCD16 estimates and that they were significantly higher than what was the case among the lean children. Among the obese boys however, SCD16 was also significantly associated with the metabolic risk score. This was not the case among the OW. The obese boys also had significantly higher fasting insulin, decreased insulin sensitivity and higher circulating TGR.

In Kang et al.'s (2017) study on the effect of a high VAT on SCD-1 estimates, they found that both the medium and high VAT group had a significantly compromised insulin health compared to the low VAT group, even though it was only the high VAT group that had significantly higher SCD-1 estimates. This may possibly correspond with Beccarelli et al.'s (2018) finding, indicating that an association between insulin function and VAT comes before becoming apparent by increasing SCD-1 indices. With regard to TGRs however, matters were different. The subjects with the significantly highest SCD-1 activity and largest VAT, also had significantly higher TGR than the other two groups. This makes sense considering that VAT is associated with an increased delivery of exogenous FAs to the liver as well increased hepatic lipogenesis and SCD-1 activity (due to MUFA synthesis), the result of which is increased release of TGRs into the bloodstream.

It may also be a question of time before improved metabolic health indicators and/or decreased adiposity are translated into significant changes in SCD-1 estimates. Rondanelli et al. (2015) investigated possible associations between SCD-1 activity and metabolic health in a metabolically healthy population. They observed that a two-month long diet intervention with ameliorations in nutritional profile and energy reduction resulted in significant reductions in BMI and abdominal fat. SCD-1 indices however were not reduced and controlling for gender and BMI did not change results. The weight reduction and diet intervention improved many other metabolic indices, among them significantly improved insulin sensitivity and normalisation of leptin levels. The lack of observable effects upon SCD-1 indices despite of the ameliorations, may have reflected that even though they were metabolically healthy before the intervention, it was a time lag before optimal metabolic balance and physiological health was restored. As such, it is possible that the anthropometric and metabolic changes that took place between baseline and follow-up would have resulted in alterations also in SCD-1 enzymatic activity in a longer time perspective. The intervention can have reduced demands on the SCD-1 enzyme and contributed to subtle changes that did not become apparent in biochemical analysis. An alternative explanation for the lack of change in SCD-1 estimates may have been that the energy restriction had increased adipose tissue lipolysis and kept SCD-1 indices elevated.

As mentioned, it in a similar study by Lee et al. (2018) it was found that even though VAT was significantly decreased, the reduction in SCD16 activity was not associated with the

decrease in VAT. It is difficult to assess if the background for these findings were comparable to Rondanelli et al.'s (2015) study since Lee et al.'s (2018) participants were metabolically unhealthy with a large VAT whereas Rondanelli et al.'s (2015) participants were metabolically healthy and most likely had a higher proportion of SAT and abdominal SAT than VAT.

In Lee et al.'s study (2018) the comprehensiveness of the intervention weakened the possibility to compare and assess possible systematic differences between the intervention group and control group, for example to isolate specific effects of the diet OR weight reduction in order to investigate their relative contribution on measured FAs and estimated SCD-1 activity. As has been demonstrated in this literature review, diet has been found to have a significant influence on SCD-1 profile independently of BMI. Similarly, it in Rondanelli et al.'s (2015) study it was difficult to assess if it was the dietary changes with less fat (and especially the reduction in SFAs) or the energy reduction that had been most influential on the observed reduction in AIs but unchanged SCD16 and SCD18. Treatment had also improved other metabolic markers (among them improved insulin and leptin function), something which may have had an effect on body mass and fat distribution. Since neither SCD16 nor SCD18 changed, but PAL was significantly reduced, reduced DNL (ie PA synthesis) is possible, perhaps due to a combination of more unrefined carbohydrates and the lower energy intake. This relationship is also a possibility in Lee et al.'s study. Since high and/or excessive intake of carbohydrates may induce the process de of DNL, the reduction of refined white rice that took place may have decreased DNL and as such reduced MUFA production and TGR synthesis. This interpretation is made more likely by the fact that DNL associated PA and SCD-1 related PAL, SA and OA were all significantly reduced between baseline and follow-up in the intervention group.

Also Svendsen et al. (2021) investigated associations between SCD-1 activity, BMI and metabolic health. They observed that while differences in SCD16 and SCD18 were significantly associated with metabolic health within BMI categories there were no differences in the association between SCD-1 estimates and BMI. In the total population, they found that the metabolically unhealthy (MU) had significantly elevated SCD16 and SCD18 activity estimates as well as significantly higher BMI. However, when splitting the metabolically healthy (MH) and MU into three categories according to BMI (NW, OW and

obese) and comparing within each BMI group, they found significant associations between metabolic health and estimated SCD-1 activity within each BMI group, but no difference in the association between SCD-1 and BMI between BMI groups. They also found a similar distribution of MH and MU within each BMI category. Neither SCD16 or SCD18 activity (nor FA profile) varied systematically between only within the three BMI groups, and within the BMI groups SCD-1 estimates varied with metabolic health. There was a trend within each BMI group however that it was the MU who had the highest BMI, and the MU NW had significantly higher BMI than the MH.

No data on neither WC nor insulin had been included among the metabolic risk factors. This is unfortunate. Increased lipid accumulation in the trunk area is regarded to be a factor of great metabolic influence as well as having an important effect on FA composition. Indeed, WC is usually included as the key components of the metabolic syndrome (Araújo et al., 2019). Even though they concluded that no interactions between SCD-1 enzyme activity estimates and BMI were observed, there was after all a small increase across the three BMI categories. Accordingly, it cannot be totally excluded that BMI had had an effect. It could also be added that the population in Svendsen et al.'s (2020) study was quite healthy since they had undergone a program on lifestyle change.

It should also be mentioned that Svendsen had estimated SCD-1 in whole blood. The choice of haematologic lipid fraction for SCD-1 estimation could possibly have affected results due to the high proportion of enterocytes in whole blood (45%). The long life span of enterocytes makes whole blood more affected by diet. This fact may especially have affected the positive association with SCD18, due to the high presence of OA in the diet. However, there were no systematic differences in dietary intake neither between nor within the BMI groups.

Also Ojwang et al. (2020) studied metabolic health, but as opposed to Svendsen found differences in lipid metabolism and SCD-1 activity both between and within BMI categories, and as such associations with SCD-1 may have been related to both metabolic health and BMI (either irrespective of or in concert with each other). The MU had significantly higher BMI, WC and WHR than the MH. Just like associations between SCD-1 and metabolic health and BMI however, possible associations between SCD-1, metabolic health and differences in body fat distribution may have affected the observed associations. However, since no correlation analysis investigating associations between SCD-1 and the different AIs had been

included, we do not know the extent to which SCD-1 activity was associated with body mass and/or other indicators of body fat distribution.

Both Svendsen et al. (2020) and Ojwang et al.'s (2020) study demonstrated that OW and obesity is not necessary to observe differences in SCD-1 activity. However, whereas Svendsen et al. (2020) found increasing SCD16 and SCD18 with increasing BMI, Ojwang et al. (2020) observed that SCD16 and SCD18 were significantly negatively associated between BMI groups whereas SCD-1 estimates were positively associated with BMI within BMI groups, but also higher among the MU within each BMI group. SCD16 however, was not significantly higher among the MU NW.

Warensjø et al. (2005) found that elevated SCD16 enzymatic activity predicted the MetS over a 20-year period, but the association disappeared when BMI was controlled for. They concluded that any apparent associations between SCD16 and risk of developing the MetS had been confounded by BMI and that the observed association was primarily explained by obesity (measured by BMI). This is especially intriguing since this was a male population. In another study Warensjø et al. (2006) as mentioned had observed that the association between SCD16 and BMI among the male participants disappeared when VAT was controlled for. Importantly, Warensjø et al. (2005) had not made specific investigations of associations with WC had not been performed (WC had not been controlled for in multiple regression analysis). We just know that the participants who developed the MetS had both significantly higher SCD16 estimates as well as significantly larger WC. Because they lacked data on WC, they had also used BMI cut-offs to calculate WC. As such the observations made by Warensjø et al. (2005) appear to be subject to uncertainty.

Not all of the studies found any associations with metabolic health. Kishino et al. (2008) in bivariate analysis found a significant positive linear relationship between SCD16 and VAT only among the OW, and not the NW subjects (according to BMI). When they analysed the OW subjects with regard to the metabolic syndrome however, they observed no significant differences between the two groups with regard to neither BMI, WC, VAT nor SCD16 and SCD18 indices. Subjects defined as having the metabolic syndrome even had somewhat lower BMI as well as smaller WC and VAT (though not significantly). Similar results between metabolic health irrespective of AIs and SCD-1 indices were seen among NW participants. Importantly however, Kishino et al. (2008) had recruited normal- and OW males most of

whom suffered from metabolic and other lifestyle-related diseases. Results may have looked completely different in a population-based study.

Following from the above-mentioned observations and reflections, it appears useful to elucidate possible associations between estimated SCD-1 activity and OW and obesity as well as abnormal fat depositions and distribution, by also considering possible associations with metabolic health variables. There are indications that SCD-1 estimates may be related to metabolic health, either independent of or in concert with excess body fat. SCD-1 estimates and abnormalities in lipid storage were found to be associated with disturbed metabolic homeostasis, with FA accumulating in areas of the body where they do not belong (the abdomen and the liver). Yet, in this literature review there were also examples of studies that found BMI to be an important metabolic risk factor. They observed associations between SCD-1 and BMI that were stronger than the associations between SCD-1 ectopic FA storage and metabolic health variables (Warensjø et al., 2005; Kishino et al., 2008; Del Pozo et al., 2020; Bonafini et al., 2020).

The reliability and validity of SCD16 and SCD18 estimates.

The even-chained SFAs that SCD-1 may desaturate and the MUFAs it may synthesise may not only come from internal processes in the liver, but also come from the diet or adipose tissue lipolysis (Peter et al., 2009; Lee et al., 2015). This explains some of the challenges involved when trying to understand endogenous FA metabolism and illustrates the need to evaluate the reliability and validity of the practice of estimating SCD-1 activity in the circulating bloodstream. It cannot be taken for granted that SCD-1 activity estimates based on biodata will accurately reflect enzyme activity (Rosqvist et al., 2022). Likewise, single or just a few measurements of plasma values for SCD-1 activity may not be representative for normal values (Vinknes, 2014, pp. 41-42).

Whether research findings based on SCD-1 ratios estimated from blood test can be trusted has been assessed by comparing estimates with more accurate results based on biopsies (Peter et al., 2009; Rosqvist et al., 2022), stable-isotope tracers (Rosqvist et al.,2019b) and deuterated water (D2O) (Lee et al., 2015). The SCD16 index has established itself as the most reliable and trusted estimation tool (Peter et al., 2009).

In a recently published paper Rosqvist et al. (2022) found that PAL and the SCD16 index was highly associated in all lipid fractions something they attributed to the low proportion of PAL in the diet. The SCD18 index was not discussed. Peter et al. (2009) found that the SCD16 index calculated from hepatic cell tissue FA composition, was significantly associated with the SCD16 index estimated in plasma VLDL-TGR as well as plasma total VLDL. The SCD18 index however was not associated.

Because OA is a frequently occurring FA in numerous food sources, the SCD18 index which is supposed to reflect endogenously synthesized OA (i.e. the conversion of SA to OA), may become diluted by a dietary intake of OA. A high SCD18 index may in effect be an indication of a healthy diet rather than reflecting the body's own synthesis of OA (Warensjø et al., 2009). High levels of circulating PAL and a high SCD16 index (PAL:PA) however, have been argued to be trustworthy because PAL is almost non-existent in food stuffs (except some marine oils and macadamia nuts) (Vinknes et al., 2013). High circulating levels of PAL will as such in most populations mirror the body's own desaturation activity.

This is the reason for why it within scientific research has been questioned whether the SCD18 index can be trusted and offers an explanation for why the SCD18 index may show opposing and somewhat confusing results (Warensjø et al., 2009). However, also the SCD16 index is vulnerable to the sources of error. This is due to the constant exchange of lipids between the hepatic and adipose lipid pools, an exchange which further emphasises the need to interpret SCD-1 estimates with care and caution.

In insulin resistance, the influence on calculated SCD-1 estimates from adipose tissue lipolysis may increase since it may become elevated also in the postprandial state (Lee et al., 2015; O'Donovan et al., 2019). Since OA is enriched in adipose tissue FFAs (in addition to dietary OA), the dilution of endogenously synthesised hepatic FAs will mainly affect the ratio of OA to SA.

The FA composition secreted from the liver in VLDL will reflect both endogenous hepatic processes like DNL and SCD-1 induced MUFA synthesis as well as exogenous sources like dietary FAs and FFAs from adipose tissue lipolysis. Hence the FA composition in hepatically assembled VLDL may not provide an exact reflection of the liver's SCD-1 activity at the time of FA measurement, due to the preceding days influence from of external FAs on hepatic cell

tissue (Peter et al., 2009). As such, hepatic SCD-1 estimates may not reflect actual endogenous SCD-1 activity.

VLDL-TGRs are synthesised in the liver from a combination of FAs that originate from adipose tissue lipolysis (62%), intra-hepatic de novo lipogenesis (23%) and dietary lipids (Stefan et al., 2008). Hepatically synthesised VLDL-TGR will not have the same FA composition as plasma total TGR or plasma total lipids (Hodson et al., 2020). According to Hodson et al. (2008), 60-70% of plasma total TGR in the fasted state typically represents VLDL-TGR.

The possible influence of choice of lipid fraction

Since calculations of hepatic SCD-1 enzymatic activity estimates are based on the calculation of product-to-precursor ratios from blood samples, SCD-1 estimates will also vary according to the chosen lipid fraction from which to calculate estimates. The FA composition is not identical between lipid fractions. Table I (enclosures) illustrates that theoretically it will for example be easier to find high SCD16 estimates when the activity is calculated from plasma CE FA composition rather than plasma PL. Due to the low relative proportion of PAL and high proportion of PA in plasma PL, a high SCD16 index in plasma PL is a quite convincing result (This description reflects my interpretation of the scientific literature I have read during my work with this literature review. Its correctness was validated in personal e-mail communication with researcher Fredric Rosqvist at the Department of Public Health and Caring Sciences, Clinical Nutrition and Metabolism, Uppsala University, April 2022). In this literature review, Steffen et al. (2008), Walle et al. (2015) and Rosqvist et al. (2017) are three examples of studies that found a significant association in CE but not in PL. Likewise, it is a notable result that of the 10 studies that had investigated the association between SCD16 and BMI in the PL lipid fraction, it was only one study (Abe) that did not find a significant association with SCD16. Compared to the SCD16 index, a high SCD18 activity index in PLs however is much less impressive due to the closer relative proportion of SA and OA respectively in the PL lipid layer ((as well as being more easily affected by diet). Saito et al. (2008) and Abe et al. (2012) found significant positive associations between SCD18 and BMI in PL.

Due to the large amount of TGR in plasma total lipids, the SCD16 and SCD18 index will when estimated in plasma total lipids be more affected by the FA composition in TGRs compared

to the FA composition in PL and CE. Plasma total lipids will also be relatively more affected by adipose tissue FA composition compared to the hepatically synthesised VLDL-TGR (Peter et al., 2009; Rosqvist et al., 2019b; Hodson et al., 2020). Even though total plasma TGR has been found to reflect liver activity, strong associations between plasma FFA and adipose tissue TGR have also been found (Warensjø et al., 2009). This suggests that the TGR lipid fraction may be influenced by the exchange of FAs between liver and adipose tissue. Also Walle et al. (2016) emphasised that FFAs is the major source of TGRs stored in the liver. This may presumably become especially relevant in an insulin resistant state. As such a person with high circulating TGR will in plasma total lipids tend to get SCD-1 estimates that are relatively more affected by adipose tissue FA composition.

Whereas Kang et al. (2017) had estimated SCD18 in plasma total lipids, Lee (2015) had chosen plasma VLDL-TGR. This may possibly contribute to explain the positive association between SCD18 and VAT observed by Kang et al. (2017) (OA from adipose tissue) and the lack of any association between SCD18 and LF in Lee et al.'s (2015) study. Interestingly, Lee found that the SCD18 index was negatively associated with both insulin resistance and high fasting insulin, whereas hepatic SA was positively associated. Recalling Stefan et al.'s (2008) findings and theory on the importance of a high SCD18 to synthesise TGR and VLDL to transport excess lipids out of liver, this is thought provoking. Adding to this, the SCD18 index in Lee et al.'s (2015) study was positively associated with insulin resistance and high fasting insulin in FFAs. This indicates a possible combination of release of adipose tissue FFAs into the circulation during lipolysis, and that this source of FAs in addition to the high hepatic lipogenesis resulted in insufficient SCD18 activity to ensure transport FAs out of the liver. However, this remains a theory and as mentioned, SCD 18 is highly susceptible to sources of error. Interestingly, all three studies they observed significant differences in SCD-1 enzymatic activity irrespectively of BMI (associations with LF by Stefan et al., 2008 and Lee et al. 2015 and VAT by Kang et al., 2017) as well as stressing an apparently close association between insulin function and abnormal FA storage. This once more illustrates an apparent need to interpret SCD-1 estimates not only in relation to body mass, but also in a larger context of metabolic health.

In their severely obese population however, Walle et al. (2016) found significant associations between SCD16 and LF and hepatic lipogenesis independently of both BMI and insulin

resistance. They emphasised that the major source of FAs that will be stored in the liver as TGRs come from adipose tissue and will become increasingly relevant in an insulin resistant state. These FAs will be closely implicated in LF build-up. However, Walle et al. (2016) found that the SCD16 index was only significantly positively associated with LF in CE, and not in TGRs. In comparison, Lee et al. (2015) found that both estimated SCD16 and measured PAL in VLDL-TGR were significantly associated with both isotopically measured lipogenesis and LF. Walle et al.'s (2016) lack of finding positive associations in TGR may have reflected that high AT lipolysis resulted in that SCD16 activity when estimated in TGR did not correctly reflect intrahepatic processes.

There is also another possibility. Since PA was significantly positively associated with LF in TGR, Walle et al. (2016) suggested that this indicated high lipogenesis and PA synthesis in the liver. This activity may have been so high that it cancelled out the activity of SCD-1 PAL synthesis and as such rendered SCD16 estimates insignificant. According to Lee et al., (2015) "…an emerging hypothesis is that the SCD-1 pathway is stimulated during lipid overload resulting from both systemic FFA delivery and hepatic DNL" (p. 41). They also argued that this activity promotes desaturation of SFAs in the liver and adipose tissue, something which may protect against lipotoxicity. They stressed the negative consequences of insufficient SCD-1 activity to deal with the SFA content due to the importance for insulin signalling and metabolic homeostasis.

In this review PAL was largely found to be associated with the same variables and outcomes as the SCD16 activity index. However, only the SCD16 index will also reflect a possible influence of DNL as well as high dietary SFAs. There were examples of associations with PA, but not SCD-1. Rondanelli et al.'s study (2015), the SCD16 index remained the same but PAL levels decreased, possibly reflecting decreased DNL due to energy reduction and/or dietary changes. Okada et al. (2005) found a positive association between PAL and FM%, but no associations with SCD16. This may perhaps indicate that PA was too high for sufficient desaturation, and that PA was instead redirected to VAT. This would fit with the observation by Rosqvist et al. (2017) that SCD16 was positively associated with SAT whereas PA was associated with VAT. This illustrates the usefulness of both measuring PAL and estimating the enzyme's activity by calculating SCD16 ratios.

Due to the assumed negative consequences of PA on insulin signalling and the important role of SCD-1 is to protect against lipotoxicity (Vessby, 2002 pp. 53–56; Lee, 2015), observations such as these strengthens the possibility of an association between lipogenesis, insulin function and SCD-1 activity. They may as such help to elucidate findings of associations between SCD-1 activity and abnormal FA accumulation and distribution instead of FA storage in SAT (and as such increasing BMI).

The association between estimated SCD-1 activity and dietary factors

The possible influence of saturated fatty acids (SFAs)

FAs have been observed to have systematic effects, having a direct influence on transcription factors that activate and deactivate lipogenic genes (Flowers & Ntambi, 2009; Vinknes, 2014, p. 44 and p. 49). As such FAs function as essential gene regulators (Jump, Tripathy & Depner, 2013; Morcillo et al., 2017; Jauregibeitia et al., 2020). Whereas polyunsaturated fatty acids (PUFAs) have been argued to have a positive and inhibiting influence the development of OW and obesity, SFAs have been suggested to upregulate obesogenic transcription factors and genes like SCD (Jump, Tripathy & Depner, 2013).

Vinknes et al. (2013) found that plasma PUFA were strongly inversely associated with both SCD16 and SCD18 estimates as well as BMI and FM. It was suggested that PUFAs may have had a positive influence on body mass and body fat regulation due to their inhibitory effect on lipogenic transcription factors and genes, including SCD. Vinknes et al. (2013) argued that high PUFA levels may favour fat oxidation in adipose tissue and the liver, as well as possibly being involved in the suppression of DNL of SFAs and the subsequent synthesis of TGRs. It was suggested that increased circulating PUFA was associated with reduced fat accumulation due to their effect on SCD-1 activity (Vinknes, 2014, p.46 and p. 54).

A positive effect of PUFAs and negative effect of SFAs was also observed by Saito et al. (2011). They found that high circulating DHA in plasma PLs decreased SCD16 estimates and significantly reduced the positive relationship between SCD16 and BMI and WHtR. They suggested that dietary DHA may have the ability to suppress high SCD-1 activity as well as improve insulin function.

In addition to FAs, hormones like insulin and leptin have been found to regulate hepatic SCD-1 gene expression and SCD-1 activity (Vessby et al., 2002; Vinknes et al., 2013). Human

studies have revealed an association between SCD-1, insulin resistance and obesity, and especially abdominal obesity (Kishino et al., 2008; Lee et al., 2015; Rosqvist et al., 2017; Alsharari et al., 2017; Kang et al. 2017; Morcillo et al., 2017; Lee et al., 2018). A high proportion of SFAs in the lipid bilayer has been found to be associated with decreased insulin sensitivity (Vessby et al., 2002; Jauregibeitia et al., 2020).

Rosqvist et al. (2014) in an intervention trial uncovered a possibly negative effect of SFAs and positive effect of PUFAs on SCD-1 regulation and body fat accumulation as well as body fat distribution. They argued that "…the fate of SFAs appears to be ectopic and general fat accumulation, whereas PUFAs instead promote lean tissue". The association between PA and excessive VAT is in accordance with Rosqvist et al.'s (2017) observations in the study included in this literature review. In that study it was found that circulating PA was significantly positively associated with having increased abdominal VAT whereas SCD16 was significantly positively associated with increased abdominal SAT. Both SCD16 and PA were positively associated with FM% and trunk fat. Rosqvist et al. (2017) assumed that high circulating PA in serum CE was at least partly derived from a dietary PA, and secondarily derived from DNL from excess carbohydrates.

The possible influence of carbohydrates

According to Flowers & Ntambi (2009) however, the liver has a unique ability to substantially increase FA synthesis in response to increased carbohydrate intake. Increased insulin secretion and SCD-1 activity will increase hepatic MUFA synthesis, and result in a combination of increased hepatic FA storage and increased transport of VLDL TGRs to adipose tissues. They stressed that sustained nutrient overload may result in excessive ectopic lipid accumulation. Compromised SAT storage capacity has been argued to be the defining characteristic of metabolically unhealthy obesity (Collins et al., 2010; Longo et al. 2019).

SCD-1 may catalyse the desaturation process of newly synthesised SFAs from DNL into various MUFAs (Alsharari et al., 2020). Just like SFAs, it has been argued that high-carbohydrate diets induce lipogenic conditions like DNL and increased SCD-1 activity (Stefan et al. 2008; Kishino et al., 2008; Chong et al., 2008; Flowers & Ntambi, 2009; Slibernagel et al., 2012; Vinknes, 2014). High levels of SFAs may increase the need for MUFA synthesis, and hence raise SCD-1 enzyme activity.

Vessby et al. (2012) showed that a low fat and high carbohydrate diet could result in higher SCD-1 index compared to a group with higher BMI. Vessby et al. (2012) assumed the women from the Shuar community had a high DNL since they had significantly higher PA, PAL, OA and SCD16 compared to the women from Lima, while simultaneously eating a very low carbohydrate diet. High SCD16 estimates were compatible with having a normal BMI and being metabolically healthy.

Among the women from Lima SCD16 was significantly associated with BMI and BF% whereas it was only associated with BMI among the women from the Shuar region. The significant relationship with BMI may have reflected a high degree of lean muscle tissue (possibly related to their active lifestyle) rather than excess fat mass. Vessby et al. (2012) suggested that the active lifestyle of the Shuar women had had a positive effect on their metabolic health. It will also have resulted in a higher degree of oxidation of SFAs, something which will have decreased the need for SCD-1 activation.

Vessby et al. (2012) argued that an increased SCD16 activity, when seen in a Western type of diet, with a higher content of fat, sugar and refined carbohydrates, usually indicates an increased SCD-1 activity in the liver associated with accumulation of LF and insulin resistance whereas a diet with a low fat content and a high proportion of non-refined carbohydrates, in connection with a high degree of physical activity, may cause increased lipogenesis and a high SCD16 activity in the adipose tissue. As such, it illustrates how a low-fat diet rich in non-refined carbohydrates can be linked to a good metabolic situation.

However, variations in response to dietary changes may influences the outcome. According to Flowers & Ntambi (2009), a low-fat, high-carbohydrate diets can affect genetic modifiers and plasma TGR levels. The Shuar women may have become genetically adjusted to an extreme high carbohydrate diet and as such had developed efficient pathways for endogenous DNL and SCD-1 processes to handle the high levels of carbohydrates. However, Vessby et al. (2012) argued that the women from the Shuar region and Lima were genetically related to such an extent this factor had been controlled for. However, the results observed among the Shuar women may not be possible to extrapolate to other populations due to their extreme lifestyle, both with regard to diet and degree of physical exercise. Furthermore, epigenetic changes may occur postnatally (Olga et al., 2021). Because the living circumstances of the two populations in Vessby et al.'s (2012) study were so different,

the study offered a unique opportunity to investigate the possible interaction between endogenous SCD-1 metabolism and diet and lifestyle.

Methodological reflections to this literature review.

The heterogeneity among the studies in this literature review with regard to study design, quality and sample size as well as the population's ethnicity, health status and age prevented that any firm conclusions could be drawn. The study design varied from representative population studies with cross-sectional data to prospective interventional case-control studies that had recruited and screened a specific study population. What the 37 included studies had in common was that they were association studies and hence not could establish any causal relationships. The associations reported varied from study to study, and some of the studies contradicted each other.

The complex and essential role of the SCD-1 enzyme and the many ways in which body fat can accumulate in the human body, made the number of and comprehensiveness of relevant factors to consider immense. A complicating factor was that the study objectives were not the same across the included studies. This resulted in that the way data on SCD-1 activity and BMI/AIs had been investigated, including how SCD-1 activity ratios had been estimated and presented, varied. The statistical tests applied to analyse data and examine possible associations differed. Only some studies had in their analysis adjusted for confounding factors, and the choice of included confounding factors and the way the testing had been performed varied (for example if BMI/AIs had been included as just one of many adjustment factors). In some of the studies it was also difficult to distinguish independent and dependent variables.

In addition to the disparities in study design and quality, the underlying biology regulating SCD-1 activity is likely highly complex. Because the activity of the enzyme appears to be closely implicated in essential physiological processes that are either indirectly or directly associated with excessive body fatness and abnormal FA storage, it seemed to be elucidating for the research question to include a decent amount of theoretical information. The number of factors that indirectly could determine SCD-1 activity, however, could be substantial.

Variations in findings both within and between studies may also be related to that the SCD-1 enzyme's role in body mass regulation may not be the same in an OW and obese population. The strength of a possible association may potentially change gradually or abruptly when moving upwards on the BMI scale. Some of the studies included all BMI categories and could investigate possible systematic differences in SCD-1 activity between OW and obese participants. Whereas some found clear associations they were absent in others.

Taken together this made it challenging to compare and contrast the findings in the studies. In the discussion (I selected to focus on) it was made an effort to investigate if it was possible to extract some commonality between the studies as well as emphasising the studies that had the highest quality in their investigation of data and had investigated associations that were of relevance for the aim of this literature study.

Had the applied inclusion criteria during the literature search been "discussion of an association between SCD-1 and overweight and obesity according to BMI" rather than just having a "BMI at or above 25", I could have selected only the articles that had focused on excessive body mass accumulation and disregarded the ones that despite of having recruited their participants on the basis of BMI, rather focused on associations between the SCD-1 enzyme and disproportionate and abnormal body fat distribution and compromised metabolic health. However, since overweight and obesity often occur simultaneously with unequally distributed body fat and the two have been found to be closely related, it would have been difficult to establish firm exclusion criteria. Many of the articles discussed both BMI and other AIs in their discussion of possible associations between SCD-1 and overweight and obesity. Also other aspects of metabolic health were frequently included. Moreover, by just applying the BMI index as inclusion criteria, and not restricting it thematically, it was possible to uncover from the literature search that individuals with similar BMI may still have differences in SCD-1 enzyme activity and that SCD-1 estimates may be similar despite different BMI.

It may even be argued that it would have been valuable to include studies among NW subjects. This would have made it possible to identify SCD-1 implicated associations that appeared not to be related to BMI and as such could have helped to uncover confounding variables also in the OW and obese segment. Since disproportionate body fat distribution and LF also may occur among NW subjects (Araújo et al., 2019), it would have been possible

to consider the extent to which potential associations between SCD-1 estimates and ectopic or LF accumulation appeared to be related, and as such not influenced by BMI. If SCD-1 estimates were not found to be related with body fat distribution in the NW segment, this could have indicated that they were rather related to some other metabolic, dietary, or other lifestyle related variable distinguishing the groups. However, there is no guarantee for that the SCD-1 enzyme's association with disproportionate body fat distribution and amount of total body fat is the same among subjects with an elevated BMI as in the NW segment. In overweight or obesity, endogenous FA metabolism and metabolic regulation may be differently affected in a NW body compared to an OW or obese body, for example due to increased vulnerability (as possibly illustrated in the study by Lee et al, 2015; Rondanelli et al., 2016; Kang et al., 2017; Beccarelli et al., 2018). As such this would have increased the scope of the study even more. It was the influence of the SCD-1 enzyme in an overweight and obese state that was the focus of this study. However, since many of the included studies had included NW participants for comparison, it was to a certain extent possible to investigate the mentioned considerations also within the chosen framework.

CONCLUSION

In this literature review, several of the included studies reported strong associations between the expression of the SCD-1 enzyme and excess body mass. However, the strength of the associations varied. There were examples of studies where SCD-1 estimates were not found to be related to variations in BMI whereas other studies presented findings of significantly different SCD-1 estimates in a population with almost matching BMI. It was also uncovered that increased SCD-1 activity is not only related to an overweight and obese state but may also be elevated and vary within a population with normal BMI. Likewise, a high BMI has been found to be compatible with normal SCD-1 activity estimates and metabolic health.

It appears that a possible association between SCD-1 activity and overweight and obesity needs to be interpreted in a larger context that includes disproportionate body fat distribution as well as aspects of metabolic health. The enzyme's activity may not be (primarily) related to overweight and obesity measured by BMI, but rather related to excessive storage of FAs in the abdominal area or the liver. However, in this literature review there were also examples of studies that found BMI to be the most important metabolic risk factor. They observed that associations between SCD-1 and BMI were stronger than the associations between SCD-1 and ectopic FA storage and metabolic health variables.

No firm conclusions could be drawn on the background of my limited material. The studies differed in thematic orientation, study design and subject characteristics. They were also association studies, precluding inference on causal relationships. To further elucidate a possible association between estimated hepatic SCD-1 activity and overweight or obesity as well as disproportionate and abnormal body fat accumulation, it is necessary with more research in different populations with variations in diet, physical activity, BMI and body composition as well as metabolic health.

REFERENCES

Abe, Y., Okada, T., Iguchi, H., Saito, E., Kuromori, Y., Iwata, F., Hara, M., Mugishima, H. & Kitamura, Y. (2012). Association of changes in body fatness and fatty acid composition of plasma phospholipids during early puberty in Japanese children. *Journal of Atherosclerosis and Thrombosis, 19*(12), 1102-1109. https://doi.org/10.5551/jat.12476.

Aglago, E. K., Biessy, C., Torres-Mejia, G., Angeles-Llerenas, A., Gunter, M. J., Romieu, I. & Chajes, V. (2017). Association between serum phospholipid fatty acid levels and adiposity in Mexican women. *Journal of Lipid Research, 58*(7), 1462-1470. https://dx.doi.org/10.1194/jlr.P073643

Alsharari, Z. D., Risérus, U., Leander, K., Sjögren, P., Carlsson, A. C., Vikström, M., Laguzzi, F., Gigante, B., Cederholm, T., De Faire, U., Hellénius, M. L., & Marklund, M. (2017). Serum Fatty Acids, Desaturase Activities and Abdominal Obesity - A Population-Based Study of 60-Year-Old Men and Women. *PloS One, 12*(1), e0170684. https://doi.org/10.1371/journal.pone.0170684

Alsharari, Z. D., Leander, K., Sjögren, P., Carlsson, A., Cederholm, T., de Faire, U., Hellenius, M. L., Marklund, M., & Risérus, U. (2020). Association between carbohydrate intake and fatty acids in the de novo lipogenic pathway in serum phospholipids and adipose tissue in a population of Swedish men. *European Journal of Nutrition, 59*(5), 2089–2097. https://doi.org/10.1007/s00394-019-02058-6

Alves-Bezerra, M., & Cohen, D. E. (2017). Triglyceride Metabolism in the Liver. *Comprehensive Physiology, 8*(1), 1–8. https://doi.org/10.1002/cphy.c170012

American Centres for Disease Control and Prevention (CDC), https://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf

Araújo J, Cai J, Stevens J. (2019). Prevalence of Optimal Metabolic Health in American Adults: National Health and Nutrition Examination Survey 2009-2016. *Metabolic Syndrome Related Disorders, 17*(1):46-52. https://doi: 10.1089/met.2018.0105.

Aune, D., Sen, A., Prasad, M., Norat, T., Janszky, I., Tonstad, S., Romundstad, P., & Vatten, L. J. (2016). BMI and all cause mortality: systematic review and non-linear dose-response meta-

analysis of 230 cohort studies with 3.74 million deaths among 30.3 million participants. *BMJ (Clinical research ed.), 353*, i2156. https://doi.org/10.1136/bmj.i2156

Baylin, A., Campos, H., (2006). The use of fatty acid biomarkers to reflect dietary intake. *Current Opinion in Lipidology. 17*(1):22-7. https://doi: 10.1097/01.mol.0000199814.46720.83.

Beccarelli LM, Scherr RE, Newman JW, Borkowska AG, Gray IJ, Linnell JD, Keen CL, Young HM. (2018). Associations Among Fatty Acids, Desaturase and Elongase, and Insulin Resistance in Children. *Journal of American College of Nutrition, 37*(1), 44-50. https://doi: 10.1080/07315724.2017.1347908.

Bianchi V. E. (2018). Weight loss is a critical factor to reduce inflammation. *Clinical nutrition ESPEN, 28*, 21–35. https://doi.org/10.1016/j.clnesp.2018.08.007

Bittner, V. (Read 23 March 2022). Impact of Gender and Life Cycle on Triglyceride Levels. Medscape Family Medicine, Triglycerides in Cardiovascular Disease Expert Column, https://www.medscape.org/viewarticle/569070

Bjermo, H., Iggman D., Kullberg Joel, Dahlman Ingrid, Johansson Lars, Persson Lena, Berglund Johan, Pulkki Kari, Basu Samar, Uusitupa Matti, Rudling Mats, Arner Peter, Cederholm Tommy, Ahlström Håkan, Risérus Ulf. (2012). Effects of n-6 PUFAs compared with SFAs on liver fat, lipoproteins, and inflammation in abdominal obesity: a randomized controlled trial, *The American Journal of Clinical Nutrition*, Volume 95, Issue 5, May, Pages 1003–1012, https://doi.org/10.3945/ajcn.111.030114

Blüher S., Mantzoros CS. Leptin in humans: lessons from translational research. Am J Clin Nutr. 2009 Mar;89(3):991S-997S. doi: 10.3945/ajcn.2008.26788E.

Bonafini, S., Giontella, A., Tagetti, A., Bresadola, I., Gaudino, R., Cavarzere, P., Ramaroli, D. A., Branz, L., Marcon, D., Pietrobelli, A., Minuz, P., Antoniazzi, F., Maffeis, C., & Fava, C. (2020). Fatty Acid Profile and Desaturase Activities in 7-10-Year-Old Children Attending Primary School in Verona South District: Association between Palmitoleic Acid, SCD-16, Indices of Adiposity, and Blood Pressure. *International journal of molecular sciences, 21*(11), 3899. https://doi.org/10.3390/ijms21113899

Cao, H., Gerhold, K., Mayers, J. R., Wiest, M. M., Watkins, S. M., & Hotamisligil, G. S. (2008). Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism. Cell, 134(6), 933–944. https://doi.org/10.1016/j.cell.2008.07.048

Choi, S. H., & Ginsberg, H. N. (2011). Increased very low density lipoprotein (VLDL) secretion, hepatic steatosis, and insulin resistance. *Trends in Endocrinology and Metabolism, 22*(9), 353–363. https://doi.org/10.1016/j.tem.2011.04.007

Choi, Y. S., Jang, H. B., Park, J. Y., Lee, H. J., Kang, J. H., Park, K. H., Lee, J. H., Park, S. I., & Song, J. (2014). Associations between estimated desaturase activity and insulin resistance in Korean boys. *Osong public health and research perspectives, 5*(5), 251–257. https://doi.org/10.1016/j.phrp.2014.08.008

Chong MF, Hodson L, Bickerton AS, Roberts R, Neville M, Karpe F, Frayn KN, Fielding BA. (2008). Parallel activation of de novo lipogenesis and stearoyl-CoA desaturase activity after 3 days of high-carbohydrate feeding. *American Journal of Clinical Nutrition. 87*(4):817-23. https://doi: 10.1093/ajcn/87.4.817.

Cohen, P., & Spiegelman, B. M. (2016). Cell biology of fat storage. *Molecular biology of the cell, 27*(16), 2523–2527. https://doi.org/10.1091/mbc.E15-10-0749

Collins JM, Neville MJ, Hoppa MB, Frayn KN. 2010. De novo lipogenesis and stearoyl-CoA desaturase are coordinately regulated in the human adipocyte and protect against palmitate-induced cell injury. *J Biol Chem. 285*(9):6044-52. https://doi: 10.1074/jbc.M109.053280.

Cornier MA, Després JP, Davis N, Grossniklaus DA, Klein S, Lamarche B, Lopez-Jimenez F, Rao G, St-Onge MP, Towfighi A, Poirier P. (2011). American Heart Association Obesity Committee of the Council on Nutrition; Physical Activity and Metabolism; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiovascular Disease in the Young; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing, Council on Epidemiology and Prevention; Council on the Kidney in Cardiovascular Disease, and Stroke Council. Assessing adiposity: a scientific statement from the American Heart Association. Circulation. Nov 1;124(18):1996-2019. https://doi: 10.1161/CIR.0b013e318233bc6a.

Cruz, M. M., Simão, J. J., de Sá, R., Farias, T., da Silva, V. S., Abdala, F., Antraco, V. J., Armelin-Correa, L., & Alonso-Vale, M. (2020). Palmitoleic Acid Decreases Non-alcoholic Hepatic Steatosis and Increases Lipogenesis and Fatty Acid Oxidation in Adipose Tissue From Obese Mice. *Frontiers in endocrinology, 11*, 537061. https://doi.org/10.3389/fendo.2020.537061

de Souza, C. O., Vannice, G. K., Rosa Neto, J. C., & Calder, P. C. (2018). Is Palmitoleic Acid a Plausible Nonpharmacological Strategy to Prevent or Control Chronic Metabolic and Inflammatory Disorders?. *Molecular nutrition & food research, 62*(1), 10.1002/mnfr.201700504. https://doi.org/10.1002/mnfr.201700504

del Genio G, Ferreri C, Marfella R, Pournaras D, le Roux CW, et al. (2015) Morbid Obesity is Associated to Altered Fatty Acid Profile of Erythrocyte Membranes. J Diabetes Metab 6: 582. doi:10.4172/2155-6156.1000582

Del Pozo, M., Lope, V., Criado-Navarro, I., Pastor-Barriuso, R., Fernández de Larrea, N., Ruiz, E., Castelló, A., Lucas, P., Sierra, Á., Romieu, I., Chajès, V., Priego-Capote, F., Pérez-Gómez, B., & Pollán, M. (2020). Serum Phospholipid Fatty Acids Levels, Anthropometric Variables and Adiposity in Spanish Premenopausal Women. *Nutrients, 12*(6), 1895. https://doi.org/10.3390/nu12061895

Do, H. J., Chung, H. K., Moon, J., & Shin, M. J. (2011). Relationship between the estimates of desaturase activities and cardiometabolic phenotypes in Koreans. *Journal of clinical biochemistry and nutrition, 49*(2), 131–135. https://doi.org/10.3164/jcbn.10-147

Engin A. (2017). The Definition and Prevalence of Obesity and Metabolic Syndrome. *Advances in experimental medicine and biology, 960*, 1–17. https://doi.org/10.1007/978-3-319-48382-5_1

Esposito, K., & Giugliano, D. (2004). The metabolic syndrome and inflammation: association or causation?. *Nutrition, metabolism, and cardiovascular diseases: NMCD, 14*(5), 228–232. https://doi.org/10.1016/s0939-4753(04)80048-6

Fabbrini, E., Magkos, F., Mohammed, B. S., Pietka, T., Abumrad, N. A., Patterson, B. W., Okunade, A., & Klein, S. (2009). Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *Proceedings of the National Academy of Sciences of the United States of America, 106*(36), 15430–15435. https://doi.org/10.1073/pnas.0904944106

Fabbrini, E., Sullivan, S., & Klein, S. (2010). Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. *Hepatology (Baltimore, Md.), 51*(2), 679–689. https://doi.org/10.1002/hep.23280

Field, A. E., Coakley, E. H., Must, A., Spadano, J. L., Laird, N., Dietz, W. H., Rimm, E., & Colditz, G. A. (2001). Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Archives of internal medicine, 161*(13), 1581–1586. https://doi.org/10.1001/archinte.161.13.1581

Flowers, M. T., & Ntambi, J. M. (2009). Stearoyl-CoA desaturase and its relation to high-carbohydrate diets and obesity. *Biochimica et biophysica acta, 1791*(2), 85–91. https://doi.org/10.1016/j.bbalip.2008.12.011

Foster, M. T., & Pagliassotti, M. J. (2012). Metabolic alterations following visceral fat removal and expansion: Beyond anatomic location. Adipocyte, 1(4), 192–199. https://doi.org/10.4161/adip.21756

Frayn, Keith N. (2010). *Metabolic Regulation. A Human Perspective* (3rd ed.). Wiley-Blackwell.

Frigolet, M. E., & Gutiérrez-Aguilar, R. (2017). The Role of the Novel Lipokine Palmitoleic Acid in Health and Disease. *Advances in nutrition (Bethesda, Md.), 8*(1), 173S–181S. https://doi.org/10.3945/an.115.011130

Fuhrman, B. J., Barba, M., Krogh, V., Micheli, A., Pala, V., Lauria, R., Chajes, V., Riboli, E., Sieri, S., Berrino, F., & Muti, P. (2006). Erythrocyte membrane phospholipid composition as a biomarker of dietary fat. *Annals of nutrition & metabolism, 50*(2), 95–102. https://doi.org/10.1159/000090496

Furtado, J. D., Beqari, J., & Campos, H. (2019). Comparison of the Utility of Total Plasma Fatty Acids Versus those in Cholesteryl Ester, Phospholipid, and Triglyceride as Biomarkers of Fatty Acid Intake. *Nutrients, 11*(9), 2081. https://doi.org/10.3390/nu11092081

García-Serrano, S., Moreno-Santos, I., Garrido-Sánchez, L., Gutierrez-Repiso, C., García-Almeida, J. M., García-Arnés, J., Rivas-Marín, J., Gallego-Perales, J. L., García-Escobar, E., Rojo-Martinez, G., Tinahones, F., Soriguer, F., Macias-Gonzalez, M., & García-Fuentes, E. (2011). Stearoyl-CoA desaturase-1 is associated with insulin resistance in morbidly obese

subjects. *Molecular medicine (Cambridge, Mass.), 17*(3-4), 273–280. https://doi.org/10.2119/molmed.2010.00078

Giontella, A., Bonafini, S., Tagetti, A., Bresadola, I., Minuz, P., Gaudino, R., Cavarzere, P., Ramaroli, D. A., Marcon, D., Branz, L., Nicolussi Principe, L., Antoniazzi, F., Maffeis, C., & Fava, C. (2019). Relation between Dietary Habits, Physical Activity, and Anthropometric and Vascular Parameters in Children Attending the Primary School in the Verona South District. *Nutrients, 11*(5), 1070. https://doi.org/10.3390/nu11051070

Global BMI Mortality Collaboration, Di Angelantonio, E., Bhupathiraju, S., Wormser, D., Gao, P., Kaptoge, S., Berrington de Gonzalez, A., Cairns, B. J., Huxley, R., Jackson, C., Joshy, G., Lewington, S., Manson, J. E., Murphy, N., Patel, A. V., Samet, J. M., Woodward, M., Zheng, W., Zhou, M., Bansal, N., … Hu, F. B. (2016). Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet (London, England), 388*(10046), 776–786. https://doi.org/10.1016/S0140-6736(16)30175-1

Gómez-Ambrosi, J., Silva, C., Galofré, J. C., Escalada, J., Santos, S., Millán, D., Vila, N., Ibañez, P., Gil, M. J., Valentí, V., Rotellar, F., Ramírez, B., Salvador, J., & Frühbeck, G. (2012). Body mass index classification misses subjects with increased cardiometabolic risk factors related to elevated adiposity. *International journal of obesity (2005), 36*(2), 286–294. https://doi.org/10.1038/ijo.2011.100

Gong, J., Campos, H., McGarvey, S., Wu, Z., Goldberg, R., & Baylin, A. (2011). Adipose tissue palmitoleic acid and obesity in humans: does it behave as a lipokine?. *The American journal of clinical nutrition, 93*(1), 186–191. https://doi.org/10.3945/ajcn.110.006502

Gray, D. S., & Fujioka, K. (1991). Use of relative weight and Body Mass Index for the determination of adiposity. *Journal of clinical epidemiology, 44*(6), 545–550. https://doi.org/10.1016/0895-4356(91)90218-x

Gruzdeva, O., Borodkina, D., Uchasova, E., Dyleva, Y., & Barbarash, O. (2019). Leptin resistance: underlying mechanisms and diagnosis. *Diabetes, metabolic syndrome and obesity: targets and therapy, 12*, 191–198. https://doi.org/10.2147/DMSO.S182406

Grønning-Wang LM, Bindesbøll, Christian, Nebb, Hilde I. (2013). The Role of Liver X Receptor in Hepatic de novo Lipogenesis and Cross-Talk with Insulin and Glucose Signalling. Lipid Metabolism. Rijeka: *InTech - Open Access Publisher.* https://www.intechopen.com/chapters/42109

Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C. L., & Anis, A. H. (2009). The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC public health, 9*, 88. https://doi.org/10.1186/1471-2458-9-88

Hauge, J. G., Aakvaag, R. K. & Christensen, T. B. (2001). *Biokjemi: en grunnbok* (4. utg.). Oslo, Universitetsforlaget.

Hiraoka-Yamamoto, J., Ikeda, K., Negishi, H., Mori, M., Hirose, A., Sawada, S., Onobayashi, Y., Kitamori, K., Kitano, S., Tashiro, M., Miki, T., & Yamori, Y. (2004). Serum lipid effects of a monounsaturated (palmitoleic) fatty acid-rich diet based on macadamia nuts in healthy, young Japanese women. *Clinical and experimental pharmacology & physiology, 31* Suppl 2, S37–S38. https://doi.org/10.1111/j.1440-1681.2004.04121.x

Hlavaty P, Tvrzicka E, Stankova B, Zamrazilova H, Sedlackova B, Dusatkova L, Hainer V, Kunesova M. 2015. Association of plasma lipids fatty acid composition with metabolic profile of Czech adolescents. *Physiological Research.;64*(Suppl 2):S167-75. doi: 10.33549/physiolres.933144. PMID: 26680477.

Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. (2008). Progress in Lipid Research 47(5), 348-80. https://doi: 10.1016/j.plipres.2008.03.003.

Hodson L, Fielding BA. Stearoyl-CoA desaturase: rogue or innocent bystander? (2013). Progress in Lipid Research 52(1), 15-42. https://doi: 10.1016/j.plipres.2012.08.002.

Hodson, L., Rosqvist, F., & Parry, S. A. (2020). The influence of dietary fatty acids on liver fat content and metabolism. The Proceedings of the Nutrition Society, 79(1), 30–41. https://doi.org/10.1017/S0029665119000569

Hodson, L., Parry, S. A., Cornfield, T., Charlton, C., Low, W. S., Green, C. J., & Rosqvist, F. (2020). Using total plasma triacylglycerol to assess hepatic de novo lipogenesis as an

alternative to VLDL triacylglycerol. *Upsala journal of medical sciences, 125*(3), 211–216. https://doi.org/10.1080/03009734.2020.1739789

Igal RA, Sinner DI. Stearoyl-CoA desaturase 5 (SCD5), a Δ-9 fatty acyl desaturase in search of a function. Biochim Biophys Acta Mol Cell Biol Lipids. 2021 Jan;1866(1):158840. https://doi: 10.1016/j.bbalip.2020.158840.

Iizuka, K., Takao, K., & Yabe, D. (2020). ChREBP-Mediated Regulation of Lipid Metabolism: Involvement of the Gut Microbiota, Liver, and Adipose Tissue. Frontiers in endocrinology, 11, 587189. https://doi.org/10.3389/fendo.2020.587189

Ipsen DH, Tveden-Nyborg P, Lykkesfeldt J. 2016. Dyslipidemia: Obese or Not Obese-That Is Not the Question. *Current Obesity Reports. 5*(4):405-412. https://doi: 10.1007/s13679-016-0232-9.

Jauregibeitia, I., Portune, K., Rica, I., Tueros, I., Velasco, O., Grau, G., Trebolazabala, N., Castaño, L., Larocca, A. V., Ferreri, C., & Arranz, S. (2020). Fatty Acid Profile of Mature Red Blood Cell Membranes and Dietary Intake as a New Approach to Characterize Children with Overweight and Obesity. *Nutrients, 12*, 3446. https://doi.org/10.3390/nu12113446

Jo, J., Gavrilova, O., Pack, S., Jou, W., Mullen, S., Sumner, A. E., Cushman, S. W., & Periwal, V. (2009). Hypertrophy and/or Hyperplasia: Dynamics of Adipose Tissue Growth. *PLoS computational biology, 5*(3), e1000324. https://doi.org/10.1371/journal.pcbi.1000324

Jump, D. B., Tripathy, S., & Depner, C. M. (2013). Fatty acid-regulated transcription factors in the liver. *Annual review of nutrition, 33*, 249–269. https://doi.org/10.1146/annurev-nutr-071812-161139

Kang, M., Lee, A., Yoo, H. J., Kim, M., Kim, M., Shin, D. Y., & Lee, J. H. (2017). Association between increased visceral fat area and alterations in plasma fatty acid profile in overweight subjects: a cross-sectional study. *Lipids in health and disease, 16*(1), 248. https://doi.org/10.1186/s12944-017-0642-z

Karlsson, M., Mårild, S., Brandberg, J., Lönn, L., Friberg, P., & Strandvik, B. (2006). Serum phospholipid fatty acids, adipose tissue, and metabolic markers in obese adolescents. *Obesity (Silver Spring, Md.), 14*(11), 1931–1939. https://doi.org/10.1038/oby.2006.225

Karpe, F., Dickmann, J. R., & Frayn, K. N. (2011). Fatty acids, obesity, and insulin resistance: time for a reevaluation. *Diabetes, 60*(10), 2441–2449. https://doi.org/10.2337/db11-0425

Kelsey, M. M., & Zeitler, P. S. (2016). Insulin Resistance of Puberty. *Current diabetes reports, 16*(7), 64. https://doi.org/10.1007/s11892-016-0751-5

Kishino, T., Watanabe, K., Urata, T., Takano, M., Uemura, T., Nishikawa, K., Mine, Y., Matsumoto, M., Ohtsuka, K., Ohnishi, H., Mori, H., Takahashi, S., Ishida, H., & Watanabe, T. (2008). Visceral fat thickness in overweight men correlates with alterations in serum fatty acid composition. *Clinical chimica acta; international journal of clinical chemistry, 398*(1-2), 57–62. https://doi.org/10.1016/j.cca.2008.08.010

Kreisberg, R. A., & Kasim, S. (1987). Cholesterol metabolism and aging. *The American journal of medicine, 82*(1B), 54–60. https://doi.org/10.1016/0002-9343(87)90272-

Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. Ageing Res Rev. 2009 Oct;8(4):339-48. doi: 10.1016/j.arr.2009.06.001. Epub 2009 Jul 1. PMID: 19576300Lee, J., Chung, D. S., Kang, J. H., & Yu, B. Y. (2012). Comparison of visceral fat and liver fat as risk factors of metabolic syndrome. *Journal of Korean medical science, 27*(2), 184–189. https://doi.org/10.3346/jkms.2012.27.2.184

Lee, J. J., Lambert, J. E., Hovhannisyan, Y., Ramos-Roman, M. A., Trombold, J. R., Wagner, D. A., & Parks, E. J. (2015). Palmitoleic acid is elevated in fatty liver disease and reflects hepatic lipogenesis. *The American journal of clinical nutrition, 101*(1), 34–43. https://doi.org/10.3945/ajcn.114.092262

Lee Y. (2015). Estimation of body size and growth patterns in Korean boys. Journal of physiological anthropology, 34(1), 20. https://doi.org/10.1186/s40101-015-0058-2

Lee, Y. J., Lee, A., Yoo, H. J., Kim, M., Kim, M., Jee, S. H., Shin, D. Y., & Lee, J. H. (2018). Effect of weight loss on circulating fatty acid profiles in overweight subjects with high visceral fat area: a 12-week randomized controlled trial. *Nutrition journal, 17*(1), 28. https://doi.org/10.1186/s12937-018-0323-4

Liu J, Han L, Zhu L, Yu Y. Free fatty acids, not triglycerides, are associated with non-alcoholic liver injury progression in high fat diet induced obese rats. Lipids Health Dis. 2016 Feb 11;15:27. doi: 10.1186/s12944-016-0194-7. PMID: 26868515; PMCID: PMC4750181.

Lysne, Vegard (2013) Langkjedede og umettede fettsyrer, read 29 May 2022 http://www.friskogfunksjonell.no/langkjedede-og-umettede-fettsyrer/

Matsuzaka T, Shimano H. Elovl6: a new player in fatty acid metabolism and insulin sensitivity. J Mol Med (Berl). 2009 Apr;87(4):379-84. doi: 10.1007/s00109-009-0449-0. Epub 2009 Mar 4. PMID: 19259639.

Morcillo, S., Martín-Núñez, G. M., García-Serrano, S., Gutierrez-Repiso, C., Rodriguez-Pacheco, F., Valdes, S., Gonzalo, M., Rojo-Martinez, G., Moreno-Ruiz, F. J., Rodriguez-Cañete, A., Tinahones, F., & García-Fuentes, E. (2017). Changes in SCD gene DNA methylation after bariatric surgery in morbidly obese patients are associated with free fatty acids. *Scientific reports, 7*, 46292. https://doi.org/10.1038/srep46292

Mozaffarian, D., Cao, H., King, I. B., Lemaitre, R. N., Song, X., Siscovick, D. S., & Hotamisligil, G. S. (2010). Circulating palmitoleic acid and risk of metabolic abnormalities and new-onset diabetes. *The American journal of clinical nutrition, 92*(6), 1350–1358. https://doi.org/10.3945/ajcn.110.003970

Muir, L. A., Neeley, C. K., Meyer, K. A., Baker, N. A., Brosius, A. M., Washabaugh, A. R., Varban, O. A., Finks, J. F., Zamarron, B. F., Flesher, C. G., Chang, J. S., DelProposto, J. B., Geletka, L., Martinez-Santibanez, G., Kaciroti, N., Lumeng, C. N., & O'Rourke, R. W. (2016). Adipose tissue fibrosis, hypertrophy, and hyperplasia: Correlations with diabetes in human obesity. Obesity (Silver Spring, Md.), 24(3), 597–605. https://doi.org/10.1002/oby.21377

Nakamura, M. T., & Nara, T. Y. (2004). Structure, function, and dietary regulation of delta6, delta5, and delta9 desaturases. *Annual review of nutrition, 24*, 345–376. https://doi.org/10.1146/annurev.nutr.24.121803.063211

National Center for Health Statistics. CDC Growth Charts: United States. 2000 [Accessed 7/06/07]. Available from http://www.cdc.gov/growthcharts/

Ni, Y., Zhao, L., Yu, H., Ma, X., Bao, Y., Rajani, C., Loo, L. W., Shvetsov, Y. B., Yu, H., Chen, T., Zhang, Y., Wang, C., Hu, C., Su, M., Xie, G., Zhao, A., Jia, W., & Jia, W. (2015). Circulating Unsaturated Fatty Acids Delineate the Metabolic Status of Obese Individuals. *EBioMedicine, 2*(10), 1513–1522. https://doi.org/10.1016/j.ebiom.2015.09.004

Ntambi J. M. (1999). Regulation of stearoyl-CoA desaturase by polyunsaturated fatty acids and cholesterol. *Journal of lipid research, 40*(9), 1549–1558.

Ntambi, J. M., & Miyazaki, M. (2004). Regulation of stearoyl-CoA desaturases and role in metabolism. *Progress in lipid research, 43*(2), 91–104. https://doi.org/10.1016/s0163-7827(03)00039-0

Nuttall F. Q. (2015). Body Mass Index: Obesity, BMI, and Health: A Critical Review. *Nutrition today, 50*(3), 117–128. https://doi.org/10.1097/NT.0000000000000092

O'Donovan, S. D., Lenz, M., Vink, R. G., Roumans, N., de Kok, T., Mariman, E., Peeters, R., van Riel, N., van Baak, M. A., & Arts, I. (2019). A computational model of postprandial adipose tissue lipid metabolism derived using human arteriovenous stable isotope tracer data. *PLoS computational biology, 15*(10), e1007400. https://doi.org/10.1371/journal.pcbi.1007400

Ohkawa, R., Low, H., Mukhamedova, N., Fu, Y., Lai, S. J., Sasaoka, M., Hara, A., Yamazaki, A., Kameda, T., Horiuchi, Y., Meikle, P. J., Pernes, G., Lancaster, G., Ditiatkovski, M., Nestel, P., Vaisman, B., Sviridov, D., Murphy, A., Remaley, A. T., Sviridov, D., … Tozuka, M. (2020). Cholesterol transport between red blood cells and lipoproteins contributes to cholesterol metabolism in blood. *Journal of lipid research, 61*(12), 1577–1588. https://doi.org/10.1194/jlr.RA120000635

Ojwang, A. A., Smuts, C. M., Zec, M., Wentzel-Viljoen, E., Kruger, I. M., & Kruger, H. S. (2020). Comparison of dietary and plasma phospholipid fatty acids between normal weight and overweight black South Africans according to metabolic health: The PURE study. *Prostaglandins, leukotrienes, and essential fatty acids, 158*, 102039. https://doi.org/10.1016/j.plefa.2019.102039

Okada, T., Furuhashi, N., Kuromori, Y., Miyashita, M., Iwata, F., & Harada, K. (2005). Plasma palmitoleic acid content and obesity in children. *The American journal of clinical nutrition, 82*(4), 747–750. https://doi.org/10.1093/ajcn/82.4.747.

Olga, van Diepen, Bobeldijk-Pastorova, Gross, Prentice, Snowden, Olga, van Diepen, Bobeldijk-Pastorova, Gross, Prentice, Snowden, Furse, Kooistra, Hughes, Schoemaker. 2021. Lipid ratios representing SCD1, FADS1, and FADS2 activities as candidate biomarkers of early

growth and adiposity. *BioMedicine, 63*, 103198. https://doi.org/10.1016/j.ebiom.2020.103198

Osadnik, K., Osadnik, T., Lonnie, M., Lejawa, M., Reguła, R., Fronczek, M., Gawlita, M., Wądołowska, L., Gąsior, M., & Pawlas, N. (2020). Metabolically healthy obese and metabolic syndrome of the lean: the importance of diet quality. Analysis of MAGNETIC cohort. *Nutrition journal, 19*(1), 19. https://doi.org/10.1186/s12937-020-00532-0

Otero, Y. F., Stafford, J. M., & McGuinness, O. P. (2014). Pathway-selective insulin resistance and metabolic disease: the importance of nutrient flux. The Journal of biological chemistry, 289(30), 20462–20469. https://doi.org/10.1074/jbc.R114.576355

Paglialunga, S., & Dehn, C. A. (2016). Clinical assessment of hepatic de novo lipogenesis in non-alcoholic fatty liver disease. *Lipids in health and disease, 15*(1), 159. https://doi.org/10.1186/s12944-016-0321-5

Paillard, F., Catheline, D., Duff, F. L., Bouriel, M., Deugnier, Y., Pouchard, M., Daubert, J. C., & Legrand, P. (2008). Plasma palmitoleic acid, a product of stearoyl-coA desaturase activity, is an independent marker of triglyceridemia and abdominal adiposity. *Nutrition, metabolism, and cardiovascular diseases: NMCD, 18*(6), 436–440. https://doi.org/10.1016/j.numecd.2007.02.017

Papamandjaris, A. A., MacDougall, D. E., & Jones, P. J. (1998). Medium chain fatty acid metabolism and energy expenditure: obesity treatment implications. *Life sciences, 62*(14), 1203–1215. https://doi.org/10.1016/s0024-3205(97)01143-0

Park, H. K., & Ahima, R. S. (2015). Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. *Metabolism: clinical and experimental, 64*(1), 24–34. https://doi.org/10.1016/j.metabol.2014.08.004

Peter, A., Cegan, A., Wagner, S., Lehmann, R., Stefan, N., Königsrainer, A., Königsrainer, I., Häring, H. U., & Schleicher, E. (2009). Hepatic lipid composition and stearoyl-coenzyme A desaturase 1 mRNA expression can be estimated from plasma VLDL fatty acid ratios. *Clinical chemistry, 55*(12), 2113–2120. https://doi.org/10.1373/clinchem.2009.127274

Petersson, H., Arnlöv, J., Zethelius, B., & Risérus, U. (2010). Serum fatty acid composition and insulin resistance are independently associated with liver fat markers in elderly men.

*Diabetes research and clinical practice, 87(*3), 379–384. https://doi.org/10.1016/j.diabres.2009.11.019

Petrus, P., Edholm, D., Rosqvist, F., Dahlman, I., Sundbom, M., Arner, P., Rydén, M., & Risérus, U. (2017). Depot-specific differences in fatty acid composition and distinct associations with lipogenic gene expression in abdominal adipose tissue of obese women. *International journal of obesity (2005), 41*(8), 1295–1298. https://doi.org/10.1038/ijo.2017.106

Picklo, M.J.; Idso, J.; Seeger, D.R.; Aukema, H.M.; Murphy, E.J. (2017). Comparative effects of high oleic acid vs high mixed saturated fatty acid obesogenic diets upon PUFA metabolism in mice, *Prostaglandins, Leukotrienes and Essential Fatty Acids, Vol.119* pp.25-37. https://www.cabdirect.org/globalhealth/abstract/20173244829

Piers, L. S., Walker, K. Z., Stoney, R. M., Soares, M. J., & O'Dea, K. (2003). Substitution of saturated with monounsaturated fat in a 4-week diet affects body weight and composition of overweight and obese men. *The British journal of nutrition, 90*(3), 717–727. https://doi.org/10.1079/bjn2003948

Piqueras P, Ballester A, Durá-Gil JV, Martinez-Hervas S, Redón J, Real JT. (2021). Anthropometric Indicators as a Tool for Diagnosis of Obesity and Other Health Risk Factors: A Literature Review. *Frontiers in Psychology, 9*;12:631179. https://doi: 10.3389/fpsyg.2021.631179.

Porter, S. A., Massaro, J. M., Hoffmann, U., Vasan, R. S., O'Donnel, C. J., & Fox, C. S. (2009). Abdominal subcutaneous adipose tissue: a protective fat depot?. *Diabetes care, 32*(6), 1068–1075. https://doi.org/10.2337/dc08-2280

Rampal, S., Mahadeva, S., Guallar, E., Bulgiba, A., Mohamed, R., Rahmat, R., Arif, M. T., & Rampal, L. (2012). Ethnic differences in the prevalence of metabolic syndrome: results from a multi-ethnic population-based survey in Malaysia. *PloS one, 7*(9), e46365. https://doi.org/10.1371/journal.pone.0046365

Rask-Andersen, M., Karlsson, T., Ek, W. E., & Johansson, Å. (2019). Genome-wide association study of body fat distribution identifies adiposity loci and sex-specific genetic effects. *Nature communications, 10*(1), 339. https://doi.org/10.1038/s41467-018-08000-4

Risé, P., Eligini, S., Ghezzi, S., Colli, S., & Galli, C. (2007). Fatty acid composition of plasma, blood cells and whole blood: relevance for the assessment of the fatty acid status in humans. *Prostaglandins, leukotrienes, and essential fatty acids, 76*(6), 363–369. https://doi.org/10.1016/j.plefa.2007.05.003

Robinson, J. (2021). What Is Metabolic Syndrome? Read 21 May 2022: https://www.webmd.com/heart/metabolic-syndrome/metabolic-syndrome-what-is-it

Rondanelli, M., Klersy, C., Perna, S., Faliva, M. A., Montorfano, G., Roderi, P., Colombo, I., Corsetto, P. A., Fioravanti, M., Solerte, S. B., & Rizzo, A. M. (2015). Effects of two-months balanced diet in metabolically healthy obesity: lipid correlations with gender and BMI-related differences. *Lipids in health and disease, 14*, 139. https://doi.org/10.1186/s12944-015-0131-1

Rosqvist, F., Iggman, D., Kullberg, J., Cedernaes, J., Johansson, H. E., Larsson, A., Johansson, L., Ahlström, H., Arner, P., Dahlman, I., & Risérus, U. (2014). Overfeeding polyunsaturated and saturated fat causes distinct effects on liver and visceral fat accumulation in humans. *Diabetes, 63*(7), 2356–2368. https://doi.org/10.2337/db13-1622

Rosqvist, F., Bjermo, H., Kullberg, J., Johansson, L., Michaëlsson, K., Ahlström, H., Lind, L., & Risérus, U. (2017). Fatty acid composition in serum cholesterol esters and phospholipids is linked to visceral and subcutaneous adipose tissue content in elderly individuals: a cross-sectional study. *Lipids in health and disease, 16*(1), 68. https://doi.org/10.1186/s12944-017-0445-2

Rosqvist, F., Kullberg, J., Ståhlman, M., Cedernaes, J., Heurling, K., Johansson, H. E., Iggman, D., Wilking, H., Larsson, A., Eriksson, O., Johansson, L., Straniero, S., Rudling, M., Antoni, G., Lubberink, M., Orho-Melander, M., Borén, J., Ahlström, H., & Risérus, U. (2019a). Overeating Saturated Fat Promotes Fatty Liver and Ceramides Compared With Polyunsaturated Fat: A Randomized Trial. *The Journal of clinical endocrinology and metabolism, 104*(12), 6207–6219. https://doi.org/10.1210/jc.2019-00160

Rosqvist, F., McNeil, C. A., Pramfalk, C., Parry, S. A., Low, W. S., Cornfield, T., Fielding, B. A., & Hodson, L. (2019b). Fasting hepatic de novo lipogenesis is not reliably assessed using circulating fatty acid markers. *The American journal of clinical nutrition, 109*(2), 260–268. https://doi.org/10.1093/ajcn/nqy304

Rosqvist, F., Fridén, M., Vessby, J., Hockings, P., Hulthe, J., Gummesson, A., Niessen, H. G., Schultheis, C., Wanders, A., Ahlström, H., Rorsman, F., & Risérus, U. (2022). Fatty acids in multiple circulating lipid fractions reflects the composition of liver triglycerides in humans. *Clinical nutrition (Edinburgh, Scotland), 41*(4), 805–809. https://doi.org/10.1016/j.clnu.2022.02.005

Saito, E., Okada, T., Abe, Y., Kuromori, Y., Miyashita, M., Iwata, F., Hara, M., Ayusawa, M., Mugishima, H., & Kitamura, Y. (2011). Docosahexaenoic acid content in plasma phospholipids and desaturase indices in obese children. *Journal of atherosclerosis and thrombosis, 18*(4), 345–350. https://doi.org/10.5551/jat.6270

Saito, E., Okada, T., Abe, Y., Odaka, M., Kuromori, Y., Iwata, F., Hara, M., Mugishima, H., & Kitamura, Y. (2014). Relationship between estimated fatty acid desaturase activities and abdominal adiposity in Japanese children. *Obesity research & clinical practice, 8*(3), e201–e298. https://doi.org/10.1016/j.orcp.2013.03.001

Sampath, H., & Ntambi, J. M. (2005). The fate and intermediary metabolism of stearic acid. *Lipids, 40*(12), 1187–1191. https://doi.org/10.1007/s11745-005-1484-z

Santoleri, D., & Titchenell, P. M. (2019). Resolving the Paradox of Hepatic Insulin Resistance. Cellular and molecular gastroenterology and hepatology, 7(2), 447–456. https://doi.org/10.1016/j.jcmgh.2018.10.016

Santosh Kumar, K.Y., Bhat, P. K., & Sorake, C. J. (2021). Double trouble: a pandemic of obesity and COVID-19. *The Lancet. Gastroenterology & hepatology, 6*(8), 608. https://doi.org/10.1016/S2468-1253(21)00190-4

Saponaro, C., Gaggini, M., Carli, F., & Gastaldelli, A. (2015). The Subtle Balance between Lipolysis and Lipogenesis: A Critical Point in Metabolic Homeostasis. *Nutrients, 7*(11), 9453–9474. https://doi.org/10.3390/nu7115475

Scherr RE, Linnell JD, Dharmar M, Beccarelli LM, Bergman JJ, Briggs M, Brian KM, Feenstra G, Hillhouse JC, Keen CL, Ontai LL, Schaefer SE, Smith MH, Spezzano T, Steinberg FM, Sutter C, Young HM, Zidenberg-Cherr S. (2017). A Multicomponent, School-Based Intervention, the Shaping Healthy Choices Program, Improves Nutrition-Related Outcomes. *Journal of Nutritional Education Behaviour 49*(5):368-379.e1., https://doi: 10.1016/j.jneb.2016.12.007.

Schiller, K., Jacobs, S., Jansen, E., Weikert, C., di Giuseppe, R., Boeing, H., Schulze, M. B., & Kröger, J. (2014). Associated factors of estimated desaturase activity in the EPIC-Potsdam study. *Nutrition, metabolism, and cardiovascular diseases: NMCD, 24*(5), 503–510. https://doi.org/10.1016/j.numecd.2013.10.029

Schnurr, T.M., Jakupović, H., Carrasquilla, G.D. et al. (2020). Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study. *Diabetologia 63*, 1324–1332, https://doi.org/10.1007/s00125-020-05140-5

Sears, B., & Perry, M. (2015). The role of fatty acids in insulin resistance. *Lipids in health and disease, 14*, 121. https://doi.org/10.1186/s12944-015-0123-1

Silbernagel, G., Kovarova, M., Cegan, A., Machann, J., Schick, F., Lehmann, R., Häring, H. U., Stefan, N., Schleicher, E., Fritsche, A., & Peter, A. (2012). High hepatic SCD1 activity is associated with low liver fat content in healthy subjects under a lipogenic diet. *The Journal of clinical endocrinology and metabolism, 97*(12), E2288–E2292. https://doi.org/10.1210/jc.2012-2152

Slawik, M., & Vidal-Puig, A. J. (2007). Adipose tissue expandability and the metabolic syndrome. *Genes & nutrition, 2*(1), 41–45. https://doi.org/10.1007/s12263-007-0014-9

Smith, G. I., Shankaran, M., Yoshino, M., Schweitzer, G. G., Chondronikola, M., Beals, J. W., Okunade, A. L., Patterson, B. W., Nyangau, E., Field, T., Sirlin, C. B., Talukdar, S., Hellerstein, M. K., & Klein, S. (2020). Insulin resistance drives hepatic de novo lipogenesis in nonalcoholic fatty liver disease. *The Journal of clinical investigation, 130*(3), 1453–1460. https://doi.org/10.1172/JCI134165

Snyder, H. (2019). Literature review as a research methodology: An overview and guidelines, *Journal of Business Research, Volume 104*, Pages 333-339, https://doi.org/10.1016/j.jbusres.2019.07.039.

Solini, A., Di Virgilio, F., Chiozzi, P., Fioretto, P., Passaro, A., & Fellin, R. (2001). A defect in glycogen synthesis characterizes insulin resistance in hypertensive patients with type 2 diabetes. *Hypertension (Dallas, Texas: 1979), 37*(6), 1492–1496. https://doi.org/10.1161/01.hyp.37.6.1492

Soon Hee Kim, Myung Sunny Kim, Myoung Sook Lee, Yong Soon Park, Hae Jeong Lee, Soon-ah Kang, Hyun Sook Lee, Kyung-Eun Lee, Hye Jeong Yang, Min Jung Kim, Young-Eun Lee, Dae Young Kwon. (2016). *Korean diet: Characteristics and historical background, Journal of Ethnic Foods*, Volume 3, Issue 1, Pages 26-31, https://doi.org/10.1016/j.jef.2016.03.002.

Staiano, A. E., & Katzmarzyk, P. T. (2012). Ethnic and sex differences in body fat and visceral and subcutaneous adiposity in children and adolescents. *International journal of obesity (2005), 36*(10), 1261–1269. https://doi.org/10.1038/ijo.2012.95

Stefan N, Peter A, Cegan A, Staiger H, Machann J, Schick F, Claussen CD, Fritsche A, Häring HU, Schleicher E. (2008). Low hepatic stearoyl-CoA desaturase 1 activity is associated with fatty liver and insulin resistance in obese humans. *Diabetologia., 51*(4):648-56. https://doi: 10.1007/s00125-008-0938-7.

Steffen, L. M., Vessby, B., Jacobs, D. R., Jr, Steinberger, J., Moran, A., Hong, C. P., & Sinaiko, A. R. (2008). Serum phospholipid and cholesteryl ester fatty acids and estimated desaturase activities are related to overweight and cardiovascular risk factors in adolescents. *International journal of obesity (2005), 32*(8), 1297–1304. https://doi.org/10.1038/ijo.2008.89

Stevens, J., Katz, E. G., & Huxley, R. R. (2010). Associations between gender, age and waist circumference. *European journal of clinical nutrition, 64*(1), 6–15. https://doi.org/10.1038/ejcn.2009.101

Sureda, A., Martorell, M., Bibiloni, M., Bouzas, C., Gallardo-Alfaro, L., Mateos, D., Capó, X., Tur, J. A., & Pons, A. (2020). Effect of Free Fatty Acids on Inflammatory Gene Expression and Hydrogen Peroxide Production by Ex Vivo Blood Mononuclear Cells. *Nutrients, 12*(1), 146. https://doi.org/10.3390/nu12010146.

Svendsen, K., Olsen, T., Nordstrand Rusvik, T. C., Ulven, S. M., Holven, K. B., Retterstøl, K., & Telle-Hansen, V. H. (2020). Fatty acid profile and estimated desaturase activities in whole blood are associated with metabolic health. *Lipids in health and disease, 19*(1), 102. https://doi.org/10.1186/s12944-020-01282-y

Tan, C. Y., & Vidal-Puig, A. (2008). Adipose tissue expandability: the metabolic problems of obesity may arise from the inability to become more obese. *Biochemical Society transactions, 36*(Pt 5), 935–940. https://doi.org/10.1042/BST0360935

The National Heart, Lung, and Blood Institute (NHLBI), Overweight and Obesity., https://www.nhlbi.nih.gov/health-topics/overweight-and-obesity, read online 140222

Thelle, Dag. (2015). *Epidemiology : a basis for public health and disease prevention*. Gyldendal akademisk, Oslo.

Zeman M, Vecka M, Burda M, Tvrzická E, Staňková B, Macášek J, Žák A. (2017). Fatty Acid Composition of Plasma Phosphatidylcholine Determines Body Fat Parameters in Subjects with Metabolic Syndrome-Related Traits. *Metabolic Syndrome Related Disorders., 15*(7):371-378. https://doi: 10.1089/met.2017.0040.

Zhou, L. Y., Deng, M. Q., Zhang, Q., & Xiao, X. H. (2020). Early-life nutrition and metabolic disorders in later life: a new perspective on energy metabolism. *Chinese medical journal, 133*(16), 1961–1970. https://doi.org/10.1097/CM9.0000000000000976

Yammine, S. G., Naja, F., Tamim, H., Nasrallah, M., Biessy, C., Aglago, E. K., Matta, M., Romieu, I., Gunter, M. J., Nasreddine, L., & Chajès, V. (2018). Association between Serum Phospholipid Fatty Acid Levels and Adiposity among Lebanese Adults: A Cross-Sectional Study. *Nutrients, 10*(10), 1371. https://doi.org/10.3390/nu10101371

Yee, J. K., Mao, C. S., Hummel, H. S., Lim, S., Sugano, S., Rehan, V. K., Xiao, G., & Lee, W. N. (2008). Compartmentalization of stearoyl-coenzyme A desaturase 1 activity in HepG2 cells. *Journal of lipid research, 49*(10), 2124–2134. https://doi.org/10.1194/jlr.M700600-JLR200

Yim, J. Y., Kim, D., Lim, S. H., Park, M. J., Choi, S. H., Lee, C. H., Kim, S. S., & Cho, S. H. (2010). Sagittal abdominal diameter is a strong anthropometric measure of visceral adipose tissue in the Asian general population. *Diabetes care, 33*(12), 2665–2670. https://doi.org/10.2337/dc10-0606

Yilmaz, M., Claiborn, K. C., & Hotamisligil, G. S. (2016). De Novo Lipogenesis Products and Endogenous Lipokines. *Diabetes, 65*(7), 1800–1807. https://doi.org/10.2337/db16-0251

Yore, M. M., Syed, I., Moraes-Vieira, P. M., Zhang, T., Herman, M. A., Homan, E. A., Patel, R. T., Lee, J., Chen, S., Peroni, O. D., Dhaneshwar, A. S., Hammarstedt, A., Smith, U., McGraw, T. E., Saghatelian, A., & Kahn, B. B. (2014). Discovery of a class of endogenous mammalian lipids with anti-diabetic and anti-inflammatory effects. *Cell, 159*(2), 318–332. https://doi.org/10.1016/j.cell.2014.09.035

Vessby, B., Gustafsson, I. B., Tengblad, S., Boberg, M., & Andersson, A. (2002). Desaturation and elongation of Fatty acids and insulin action. *Annals of the New York Academy of Sciences, 967*, 183–195. https://doi.org/10.1111/j.1749-6632.2002.tb04275.x

Vessby B, Ahrén B, Warensjö E, Lindgärde F. Plasma lipid fatty acid composition, desaturase activities and insulin sensitivity in Amerindian women. (2012). *Nutritional Metabolic Cardiovascular Disease, 22*(3):176-81. https://doi: 10.1016/j.numecd.2010.07.011.

Vinknes KJ, Elshorbagy AK, Nurk E, Drevon CA, Gjesdal CG, Tell GS, Nygård O, Vollset SE, Refsum H. (2013) Plasma stearoyl-CoA desaturase indices: association with lifestyle, diet, and body composition. *Obesity, 21*(3), https://doi: 10.1002/oby.20011. PMID: 23404690.

Vinknes, K. J., Elshorbagy, A. K., Drevon, C. A., Nurk, E., Tell, G. S., Nygård, O., Vollset, S. E., & Refsum, H. (2013). Associations between plasma polyunsaturated fatty acids, plasma stearoyl-CoA desaturase indices and body fat. *Obesity (Silver Spring, Md.), 21*(9), E512–E519. https://doi.org/10.1002/oby.20457

Vinknes, K. J. (2014). *Fatty acid profile and body composition*, Dissertation for the degree of Philosophiae Doctor (Ph. D), Faculty of Medicine, University of Oslo, Oslo.

Virtue, S., & Vidal-Puig, A. (2010). Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome--an allostatic perspective. Biochimica et biophysica acta, 1801(3), 338–349. https://doi.org/10.1016/j.bbalip.2009.12.006

Walle, P., Takkunen, M., Männistö, V., Vaittinen, M., Lankinen, M., Kärjä, V., Käkelä, P., Ågren, J., Tiainen, M., Schwab, U., Kuusisto, J., Laakso, M., & Pihlajamäki, J. (2016). Fatty acid metabolism is altered in non-alcoholic steatohepatitis independent of obesity. *Metabolism: clinical and experimental, 65*(5), 655–666. https://doi.org/10.1016/j.metabol.2016.01.011

Wang, Z., Wang, D. H., Park, H. G., Yan, Y., Goykhman, Y., Lawrence, P., Kothapalli, K., & Brenna, J. T. (2019). Identification of genes mediating branched chain fatty acid elongation. *FEBS letters, 593*(14), 1807–1817. Retrieved from https://doi.org/10.1002/1873-3468.13451

Warensjø E, Risérus U, Vessby B. (2005) Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men. *Diabetologia; 48*(10):1999-2005. https://doi: 10.1007/s00125-005-1897-x.

Warensjø, E., Ohrvall, M., & Vessby, B. (2006). Fatty acid composition and estimated desaturase activities are associated with obesity and lifestyle variables in men and women. *Nutrition, metabolism, and cardiovascular diseases: NMCD, 16*(2), 128–136. https://doi.org/10.1016/j.numecd.2005.06.001

Warensjø, E., Ingelsson, E., Lundmark, P., Lannfelt, L., Syvänen, A. C., Vessby, B., & Risérus, U. (2007). Polymorphisms in the SCD1 gene: associations with body fat distribution and insulin sensitivity. *Obesity (Silver Spring, Md.), 15*(7), 1732–1740. https://doi.org/10.1038/oby.2007.206

Warensjø E, Risérus U, Gustafsson IB, Mohsen R, Cederholm T, Vessby B. (2008). Effects of saturated and unsaturated fatty acids on estimated desaturase activities during a controlled dietary intervention. *Nutrition, Metabolism and Cardiovascular Diseases, 18*(10):683-90. doi: 10.1016/j.numecd.2007.11.002.

Warensjø, E., Rosell, M., Hellenius, M. L., Vessby, B., De Faire, U., & Risérus, U. (2009). Associations between estimated fatty acid desaturase activities in serum lipids and adipose tissue in humans: links to obesity and insulin resistance. *Lipids in health and disease, 8*, 37. https://doi.org/10.1186/1476-511X-8-37

Washington University School of Medicine. (2009, August 25). Fat In The Liver -- Not The Belly -- May Be A Better Marker For Disease Risk. ScienceDaily. Retrieved from www.sciencedaily.com/releases/2009/08/090824151304.htm

Wolters, M., Schlenz, H., Foraita, R., Galli, C., Risé, P., Moreno, L. A., Molnár, D., Russo, P., Veidebaum, T., Tornaritis, M., Vyncke, K., Eiben, G., Iacoviello, L., Ahrens, W., & IDEFICS consortium (2014). Reference values of whole-blood fatty acids by age and sex from

European children aged 3-8 years. *International journal of obesity (2005), 38* Suppl 2(Suppl 2), S86–S98. https://doi.org/10.1038/ijo.2014.139

Wolters, M., Schlenz, H., Börnhorst, C., Risé, P., Galli, C., Moreno, L. A., Pala, V., Siani, A., Veidebaum, T., Tornaritis, M., Fraterman, A., de Henauw, S., Marild, S., Molnar, D., Ahrens, W., & IDEFICS Consortium (2015). Desaturase Activity Is Associated With Weight Status and Metabolic Risk Markers in Young Children. *The Journal of clinical endocrinology and metabolism, 100(*10), 3760–3769. https://doi.org/10.1210/jc.2015-2693

Wolters, M., Börnhorst, C., Schwarz, H., Risé, P., Galli, C., Moreno, L. A., Pala, V., Russo, P., Veidebaum, T., Tornaritis, M., Fraterman, A., De Henauw, S., Eiben, G., Lissner, L., Molnár, D., & Ahrens, W. (2017). Association of desaturase activity and C-reactive protein in European children. *Pediatric research, 81*(1-1), 27–32. https://doi.org/10.1038/pr.2016.186

World Health Organization (WHO). Obesity and overweight. (2021). Retrieved from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

World Health Organization (WHO). Regional Office for Europe. (2022). WHO European Regional Obesity Report. (2022). World Health Organization. Regional Office for Europe. Retrieved from https://apps.who.int/iris/handle/10665/353747.

UniProtKB Database, Protein: Elongation of very long chain fatty acids protein 3, Gene: Elovl3, last modification 23 February 2022. Retrieved from https://www.uniprot.org/uniprot/O35949

ENCLOSURES

FIGURES

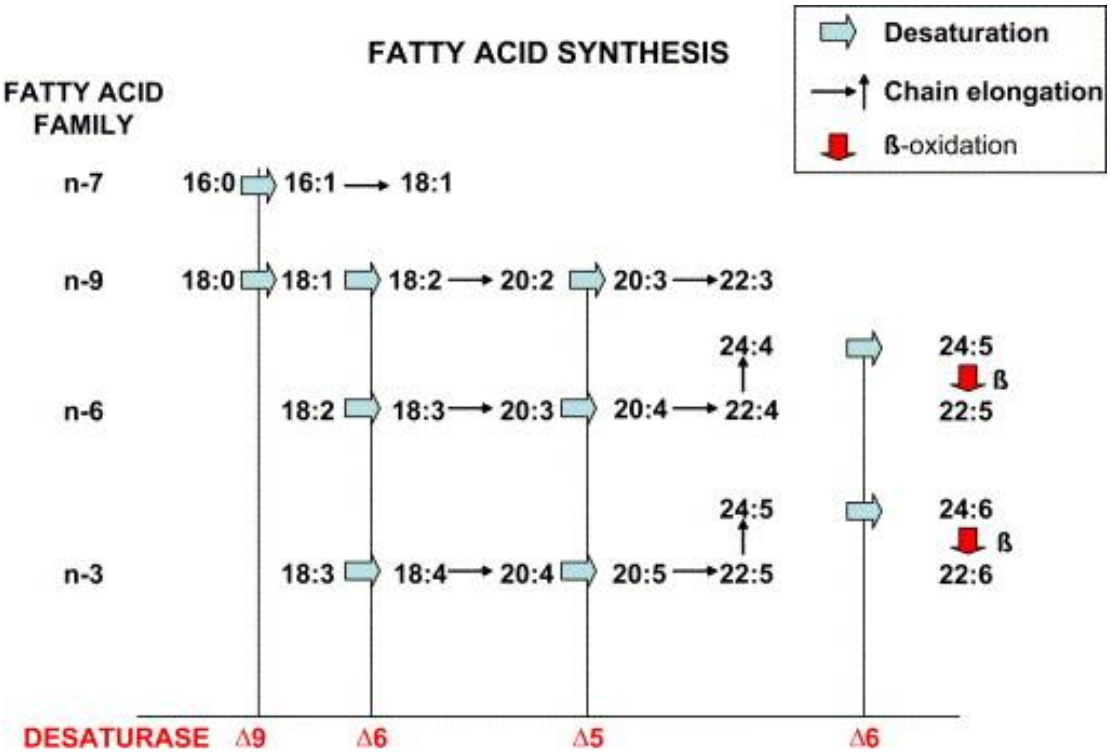

Figure I.

An illustration of the SCD-1 enzyme's cellular metabolic pathways in MUFA synthesis.

From Warensjö E, Risérus U, Gustafsson IB, Mohsen R, Cederholm T, Vessby B. (2006). Warensjö, E., Ohrvall, M., & Vessby, B. (2006). Fatty acid composition and estimated desaturase activities are associated with obesity and lifestyle variables in men and women. *Nutrition, metabolism, and cardiovascular diseases: NMCD, 16*(2), 128–136

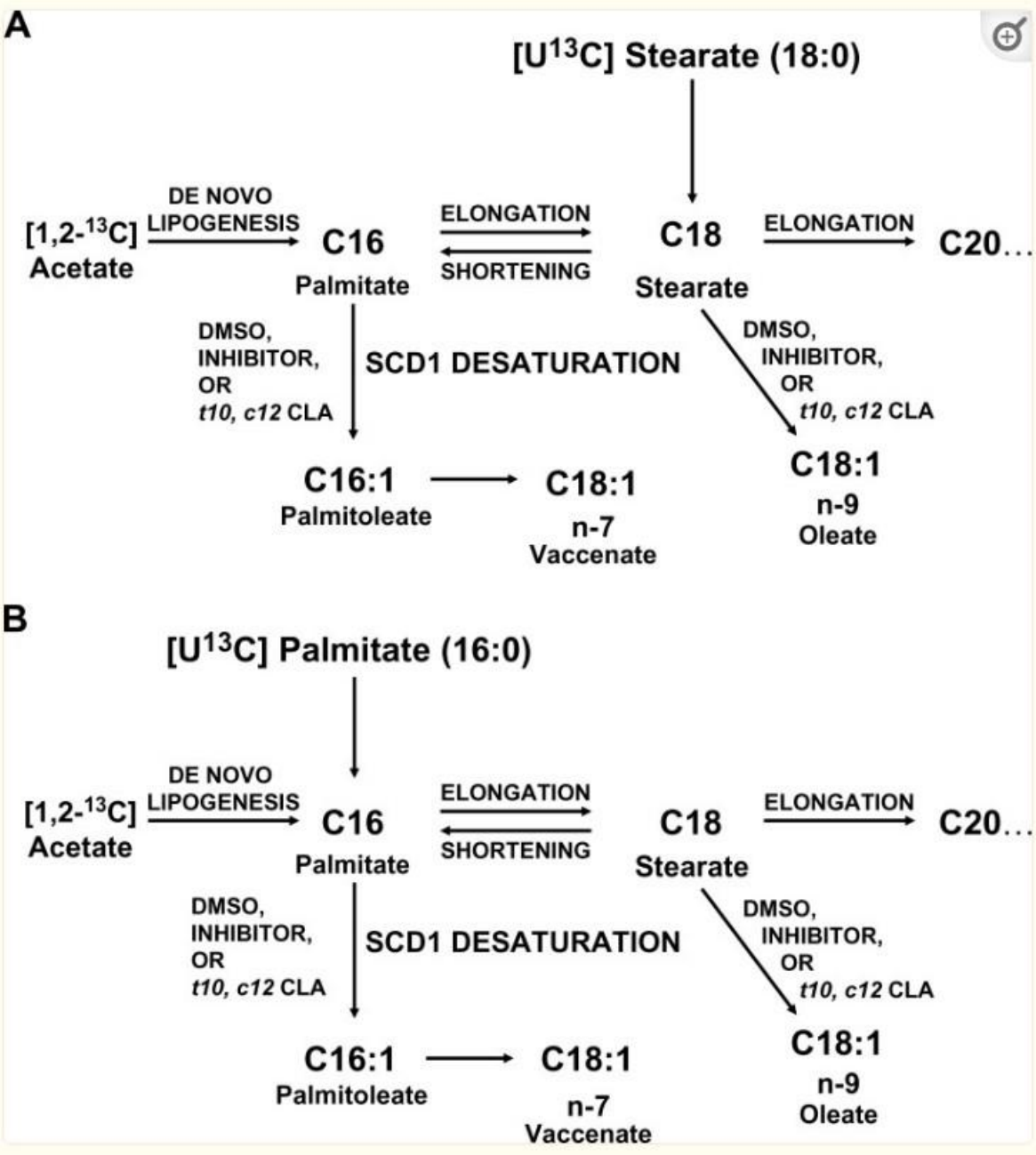

Figure II

An illustration of the SCD-1 enzyme's cellular metabolic pathways in MUFA synthesis.

From Yee, J. K., Mao, C. S., Hummel, H. S., Lim, S., Sugano, S., Rehan, V. K., Xiao, G., & Lee, W. N. (2008). Compartmentalization of stearoyl-coenzyme A desaturase 1 activity in HepG2 cells. *Journal of lipid research, 49*(10), 2124–2134.

TABLES

Table I

Hepatic cell tissue and adipose cell tissue FA composition.

	Adipose tissue	Plasma FFAs	Plasma TAG	Plasma PL	Plasma CE	Plasma total FAs	Erythrocyte PL FAs
PA	21.5	28.3	29.5	31.3	13.6	23.0	20.8
PAL	7.2	4.1	5.1	1.0	4.0	2.8	1.1
SA	3.4	12.5	4.5	14.3	1.3	7.6	18.7
OA	43.5	32.7	37.7	10.1	19.3	19.5	17.0

Based on Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. 2008. *Progress in Lipid Research 47*(5), 348-80. https://doi: 10.1016/j.plipres.2008.03.003

Table II

A quick guide.

The association between estimated enzymatic SCD-1 activity and overweight or obesity, including various forms of abnormal lipid accumulation.

Associated?	Associated	Partially associated	Potentially associated	Not associated
1.Beccarelli, 2018.				X
2.Hlavaty, 2015.		X		
3.Okada, 2015.	X			
4. Choi, 2014.	X			
5.Abe, 2012.	X			
6. Morcillo, 2017.	X			
7.Kang, 2017.	X			
8.Wolters, 2015.	X			
9.Steffen, 2008.		X		
10. Rondanelli, 2015.		X		
11. Saito, 2011	X			
12. Saito, 2014	X			
13. Zeman, 2017.	X			
14. Aglago, 2017.	X			
15. Ojwang, 2020.	X			
16. Vessby, 2012.	X			
17. Del Pozo, 2020.		X		
18. Lee, 2018.			X	
19. Paillard, 2008.			X	
20. Svendsen, 2020.				X

21. Schiller, 2014.	X			
22. Warensjø, 2005.	X			
23. Warensjø, 2006.	X			
24. Warensjø, 2009.	X			
25. Vinknes, 2013.	X			
26. Bonafini, 2020.	X			
27. Yammine, 2018.	X			
28. Jauregibeita, 2020.	X			
29. Kishino, 2008.	X			
30. Do, Chung, Moon & Shin, 2011.	X			
31. Alsharari, 2017.	X			
36. Walle, 2016.	X			
33. Lee, 2015.	X			
32. Petersson, 2018.	X			
34. Rosqvist, 2017.	X			
35. Silbernagel, 2012.	X			
37.Stefan, 2008.	X			
TOTAL	27	5	3	2

Table III

1.The association between estimated enzymatic SCD-1 activity and overweight or obesity

Title	Definitions	Particiapnt BMI	BMI	WC, WtHR	VAT, WHR or SAD	Liver fat Body fat	Associations
1. Associations Among Fatty Acids, Desaturase and Elongase, and Insulin Resistance in Children, Beccarelli et al., 2018.	Categorized in the weight categories NW, OW or OB according to age and gender specific BMI percentiles determined by the American Centres for Disease Control and Prevention (CDC).	NW OW OB					SCD16 and SCD18: No significant associations with BMI -Associations between SCD-1 and WC or WHR was not investigated in statistical analysis. Both indicators increased with increasing BMI.
2. Association of Plasma Lipids Fatty Acid Composition with Metabolic Profile of Czech Adolescents, Hlavaty et al., 2015	Categorized in the weight categories NW, OW or OB according to age and gender specific BMI percentiles. -Normal BMI between the 25th and 75th percentile, overweight BMI between the 75th and 95th percentile and obese BMI above the 95th percentile.	NW OW OB				P BF%	SCD16: -No significant association with BMI. -Significant positive association with BF%. SCD18: -No significant association with BMI nor BF%.
3. Plasma palmitoleic acid content and obesity in children, Okada et al., 2005	Obesity defined as RW >120% of predicted for gender, age, and height according to defined standards from the Japanese Ministry of Health, Labour and Welfare.	NW OB	P		P WHR		SCD16: -SCD16: Significantly positively associated with BMI. -SCD16: Significantly positively associated with WHR.

	-Analysed in two groups, non-obese and obese.						-SCD16: Not significantly associated with BF%.
4. Associations Between Estimated Desaturase Activity and Insulin Resistance in Korean Boys, Choi et al., 2014.	-Recruited participants from a cohort study on identification of early risk factors for obesity and associated metabolic disease. -Obese defined as having a BMI greater than the 85th percentile for age and gender based on Korean child growth standards. -Second phase: The intermediate group had BMI values in the 60–85% percentile in terms of obesity. -The metabolic risk score was computed by adding their scores on the following factors: BMI, BP, TAG, HDL-C and IR.	NW OW (phase 2) OB	P1	P WC 1			Baseline: -SCD-16: Significantly positively associated with BMI, WC and a metabolic risk score. Follow-up: -SCD16: In the total population it was positively, but not significantly, associated with BMI, WC and the metabolic risk score. -SCD16 was equally high between overweight and obese boys, and they had significantly higher SCD16 the compared to the lean boys. -SCD-18: No significant associations, but a negative direction of the relationship with BMI, WC and the metabolic risk score.
5. Association of Changes in Body Fatness and Fatty Acid Composition of Plasma Phospholipids during early Puberty in Japanese Children, Abe et al., 2012	Calculated RW according to the standard weight for gender, age and hight using data from the Ministry of Education, Science, Sports and Culture.	NW OB	N*a	N*a WtHR			-SCD16: No significant association with RW -SCD16: No significant association with WHtR. -SCD18: Significantly negatively associated with RW among boys. - SCD18: Significantly negatively associated with WHtR among boys.
6.	Laparoscopic Roux-en Y gastric by-pass (RYGB)	OB MOB	P, P*	P, P* WC			SCD16 and SCD18:

Changes in SCD gene DNA methylation after bariatric surgery in morbidly obese patients are associated with free fatty acids, Sonsoles Morcillo et al., 2017	-Associations reflect a comparison of the intervention group's SCD-1 enzymatic activity estimates before and six months after bariatric surgery -Control group comprised of obese subjects with a similar BMI and insulin sensitivity to that found in a group of previously morbidly obese subjects six months after RYGB.						-Significant positive association with BMI and WC -Significantly decreased SCD-1 enzymatic activity and increased SCD methylation promoter were only experienced by the participants who lost the most weight (above the 75th percentile).
7. Association between increased visceral fat area and alterations in plasma fatty acid profile in overweight subjects: a cross-sectional study, Kang et al., 2017	The participants were sorted in three groups according to the thickness of their VAT (T1 (highest), T2 and T3 (lowest)) and the exact BMI of each group was determined.	OW	Not investigated.		P, P* VAT		SCD16 and SCD18 BMI: Not investigated. VAT: Significant positive association.
8. Desaturase Activity Is Associated With Weight Status and Metabolic Risk Markers in Young Children, Wolters et al., 2015	-The children were sorted in three groups according to BMI (thin, NW, OW or OB); cut-off points for the BMI groups not specified. -Health examinations at baseline and after two years. -At baseline the children were allocated to either an intervention group to promote	NW OW OB	P				-Significant positive association between SCD16 and BMI both at baseline and after two years. -The strength of the association between SCD16 and BMI was weakened between baseline and follow-up. -SCD18: Not estimated.

	the adoption of a obesity-preventing healthy lifestyle or a control group. -To isolate the effect of FA and SCD16 metabolism on anthropometric and metabolic indicators two years later, the possible effect of the intervention program was adjusted for.						
9. Serum phospholipid and cholesteryl ester fatty acids and estimated desaturase activities are related to overweight and cardiovascular risk factors in adolescents, Steffen et al., 2008	-Age and gender specific BMI percentiles. -Categorized as NW or OW (at or above the 85th percentile) according to cut-off points determined by the American Centres for Disease Control and Prevention (CDC).	NW OW	P	P (WC)			-In bivariate analysis SCD16 was significantly positively associated with BMI in CE, but not in PL. -The significant association between SCD16 and BMI and WC as lost in multiple regression analysis together with other cardiovascular risk factors.
10. Effects of two-months balanced diet in metabolically healthy obesity: lipid correlations with gender and BMI-related differences, Rondanelli et al, 2015.	-To be classified as MHO they had values within the normal range in the following categories 1. TGRs, 2. Cholesterol 3.+4. Lipoproteins (HDL and LDL) and 5. Insulin. -Analysed the material according to BMI below and above 30. -Subjects were provided plans for dietary changes according	OW OB	P*				At baseline: -Women had significantly lower SCD16 and SCD18 than men. -SCD18 was significantly negatively associated with BMI. SCD16 was not associated but had a negative direction. At follow-up after two months with energy restricted diet intervention: -Significant reductions in BMI and android fat mass, but no changes in estimated

	to the American Diabetes Association. -Individual diet plans designed for weight loss of 0.5 to 1 kg per week.						SCD16 nor SCD18 activity (controlling for BMI and gender did not change results). -Significant reduction in PAL.
11. Docosahexaenoic Acid (DHA) Content in Plasma Phospholipids and Desaturase Indices in Obese Children, Saito et al., 2011	-All children had abdominal obesity (measured by WHtR), and five qualified for MetS. -MetS was defined as having two of the following in addition to abdominal obesity: dyslipidaemia, elevated glucose or elevated BP. -Obesity was defined as relative body weight greater than 120% of the standard weight for gender, age and height.	OW	P, P*	P WtHR			-SCD16 and SCD18: Significantly positively associated with BMI. -SCD16 (but not SCD18): Significantly positively associated with WHtR.
12. Relationship between estimated fatty acid desaturase activities and abdominal adiposity in Japanese children, Saito et al., 2014	- Percentage OW (POW) was calculated according to the standard weight obtained for gender, age and height. Obesity was defined as having a percentage OW above 20%. -Abdominal obesity was defined as having a waist to height ratio (WHtR) above 0.5.	NW OB	Not investigated.	NW: N* OB: P* WtHR			-Total population: SCD18 was negatively associated with WHtR. -When sorted in two groups according to degree of abdominal obesity: SCD18 activity had a U-shaped association with WHtR: -SCD18 was significantly negatively associated with WHtR among children without abdominal obesity children. -SCD18 was significantly positively associated with WHtR among children with abdominal obesity.

							-POW was significantly higher among children with abdominal obesity.
13. Fatty Acid Composition of Plasma Phosphatidylcholine Determines Body Fat Parameters in Subjects with Metabolic Syndrome-Related Traits, Zeman et al., 2017	-Two groups of participants were recruited, a study group with MetS related traits and a healthy control group. -In the study group 83 % of the participants had central obesity and at least one other component of the MetS as defined by the International Diabetes Federation.	NW OW	?P	?P (WC)	?P (WHR)	?BF%	-The overweight study group with significantly higher SCD16 and MetS related traits, also had significantly higher BMI, WC, WHR and BF%. -SCD16 was significantly positively associated with having MetS related traits. - SCD18: Not associated.
14. Associations between serum phospholipid fatty acid levels and adiposity in Mexican women, Aglago et al., 2017		OB	P, N*	P, N* (WC)			-SCD16: significantly positively associated with BMI and WC, but the association with WHR did not reach significance. -SCD18: significantly negatively associated with BMI and WC, but not with WHR. Significance was lost when tested for false discovery rate.
15. Comparison of dietary and plasma phospholipid fatty acids between normal weight and overweight black South Africans according to metabolic health: The PURE study, Ojwang et al., 2019	-Participants were categorised as metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight/obese (MHO) and metabolically unhealthy overweight/obese (MUO). -MetS defined as having abnormalities in three or more	NW OW OB	N, N*	?P WC	WHR?		-The MUNW, MHO, and MUO had significantly higher BMI, WC and WHR than the MHNW. -Between BMI-groups, SCD16 and SCD18 were significantly negatively associated with BMI. - Within BMI groups, SCD16 and SCD18 were positively associated with BMI. - Within BMI-groups, SCD16 and SCD18 were negatively associated with metabolic health.

	of the following criteria: 1. Glucose regulation, 2. TGR, 3. Lipoprotein composition, 4. BP or 5. Large WC						
16. Plasma lipid fatty acid composition, desaturase activities and insulin sensitivity in Amerindian women, Vessby et al., 2010	Three different groups of women, the genetically related women from the Amazonian Shuar region and Peruvian capital Lima, as well as a Swedish reference group.	NW OW	P			P (BF%)	-SCD16: Significantly positively associated with BMI among all women. -The women from Lima had the highest BMI and the strongest association with BMI despite of that the women from the Shuar region had significantly higher PA, PAL, OA and SCD16 compared to the women from Lima. -SCD16: significantly positively associated with BF% among the women from Lima, but not the women from the Shuar region.
17. Serum Phospholipid Fatty Acids Levels, Anthropometric Variables and Adiposity in Spanish Premenopausal Women, Del Pilar del Pozo et al., 2020	Associations between SCD16 and SCD18 with anthropometric indices were calculated by comparing women in the 80th percentile with women in the 20th percentile of each desaturation index.	OW	P, N*	N* (WC)			-SCD16: significantly positively associated with BMI. -SCD18: significantly negatively associated with BMI and significantly positively with WC. -SCD16: Weight Gain Since Age 18, Body Fat Percentage and VAT were not significantly associated after adjustment for BMI.
18. Effect of weight loss on circulating fatty acid profiles in overweight subjects with high visceral fat area: a 12-week	-Subjects were divided into two groups: a weight-loss group with 12 weeks of mild calorie restriction (a 300 kcal/day intake reduction) or a control group with no treatment. -Randomized controlled trial	OW	?P	?P (WC)		?FM% and FM.	-Weight loss was significantly associated with reduction of BMI, WC, VAT, FM% and FM. -After the intervention and adjusted for baseline values, SCD16 activity, PA, PAL, SA and OA were significantly decreased in the weight-loss group.

randomized controlled trial, Lee et al., 2018							-The decrease VAT was significantly positively associated with reductions in weight, BMI, WC, FM% and FM as well as insulin regulation, but not with SCD16. -SCD18 was not associated.
19. Plasma palmitoleic acid, a product of Stearoyl-CoA desaturase activity, is an independent marker of triglyceridemia and abdominal adiposity, Paillard et al., 2008	-The study population was analysed according to plasma TGR percentiles, below 75th or at or above 75th percentile. -Abdominal obesity was defined as WC < or ≥95 cm.	NW OW	?P	?P (WC)			-SCD16: significantly increased in the high TGR group. -The high TGR group also had significantly higher BMI and WC as well as significantly higher PA, PAL and OA. -PAL was significantly positively associated with WC, but significane was lost when TGRs was added among the independent variables. -SCD18: not significantly different in the high or low TG group.
20. Fatty acid profile and estimated desaturase activities in whole blood are associated with metabolic health* Svendsen et al., 2020	Participants were classified as MH if they had normalised TG levels, total cholesterol, LDL and HDL as well as glucose regulation.	NW OW OB					-SCD16 and SCD18 were not associated with BMI -SCD16 and SCD18 were significantly negatively associated with metabolic health in all three BMI categories.
21. Associated factors of estimated desaturase activity in the EPIC-Potsdam study, Schiller et al., 2014	Data analysed as quintiles of SCD16 activity estimates according to BMI, WC and WHR.	NW OW	P		P (WHR)		-SCD16 positive association with BMI and WHR.

22. Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men, Warensjø et al., 2005.	Compared AIs (BMI and WC) and metabolic indicators, as well as FA composition and SCD-1 activity estimates, between those who did and did not develop the MetS between baseline and follow-up (twenty years later). -To classify as having developed the MetS three or more risk factors had to be present: 1. Glucose, 2. BP, 3. TGR level, 4.Cholesterol and/or 5.Elevated WC.	NW OW	P	?WC			-SCD16: significantly positively associated with BMI. -SCD16: significantly associated with the development of the metabolic syndrome, but the association was confounded by BMI. -The exact association between SCD16 and WC is unknown. -For each standard deviation increase in SCD16 activity the risk of having developed the metabolic syndrome between baseline and follow-up increased by 30%. -SCD18: not associated.
23. Fatty acid composition and estimated desaturase activities are associated with obesity and lifestyle variables in men and women, Warensjø et al., 2006.		NW OW	P	P (WC)	P (SAD)		-SCD16: significantly positively associated with BMI, VAT (measured as SAD) and WC. -Among women the significant association between SCD16 and VAT was lost when BMI was adjusted for, but it remained among men. -In logistic regression the OR for having high BMI increased by 50–60% for each SD increase in SCD16. - SCD18: not associated.
24. Associations between estimated fatty acid desaturase activities in		NW OW	P, N*				-SCD16 was significantly positively associated with BMI in serum PLs and AT-TGR, but not in serum FFAs.

serum lipids and adipose tissue in humans: links to obesity and insulin resistance, Warensjø et al., 2009							-SCD18 was significantly positively associated with BMI in serum FFAs and AT-TGR, but was inversely associated in serum PLs.
25. Plasma stearoyl-CoA desaturase indices: Association with lifestyle, diet, and body composition, Vinknes et al., 2012.		NW OW OB	P, P*			P, P* BF	-Plasma SCD16 and SCD18 indices were significantly positively associated with BMI and FM (adjusted for confounding factors). -The OR for having high BMI and high FM% increased with increasing quintiles of plasma SCD-1 indices.
26. Fatty Acid Profile and Desaturase Activities in 7–10-Year-Old Children Attending Primary School in Verona South District: Association between Palmitoleic Acid, SCD-16, Indices of Adiposity, and Blood Pressure, Bonafini et al.	-The children were sorted in a normal weight or excess weight group according to BMI (age and gender adjusted) -The excess weight group was comprised of obese children (BMI ≥ 95th percentile) and overweight children (BMI ≥ 85–95th percentile)	NW OW OB	P, N*	P, N* (WtHR)		P, N* (FM)	-In the total population BMI, WtHR and FM were significantly positively associated with SCD16, but WtHR and FM lost significance with adjustment for BMI. -PAL and SCD16: significantly higher in the excess weight group compared to the normal weight group. SCD18 was not significantly different. -Among excess weight children BMI, WtHR and FM were significantly positively associated with SCD16 and PAL after adjustment, but WtHR and FM lost significance when BMI was added as adjustment factor. -Among normal weight children BMI, WtHR and FM were significantly positively associated with PAL and SCD16, but WtHR

							and FM lost significance already before BMI was added to the adjustment model. -Most associations between anthropometric indicators and SCD18 were negative, but lost significance with adjustment.
27. Association between Serum Phospholipid Fatty Acid Levels and Adiposity among Lebanese Adults: A Cross-Sectional Study, Yammine et al., 2018		NW OW OB	P, N*	P, N* (WC)			Significant associations between SCD16 and SCD18 and anthropometric indicators were only seen among women: -SCD16 was significantly positively associated with BMI and WC, but lost significance when tested for false discovery rate. -SCD18 was significantly negatively associated with both BMI and WC. -Differences between men and women were significantly different for the SCD18 index, but SCD16 was not significantly different when comparing results for men and women.
28. Fatty Acid Profile of Mature Red Blood Cell Membranes and Dietary Intake as a New Approach to Characterize Children with Overweight and Obesity, Jauregibeitia et al., 2020	The children were classified as NW, OW or OB according to BMI (age and gender adjusted). They were classified as: -normal weight when BMI was −1 < the standard deviation (SD) ≤ +1, -overweight when BMI was +1 < SD ≤ +2		N*				-The SCD16 index did not differ between normal weight, overweight and obese children. -The SCD18 index was significantly negatively associated with BMI. - The normal weight had significantly higher SCD18 than the overweight and obese, but the overweight did not have significantly higher SCD18 than the obese.

	-obese when BMI was SD > +2						
29. Visceral fat thickness in overweight men correlates with alterations in serum fatty acid composition, Kishino et al., 2008	-Participants were classified as having or not having the MetS based on their measured WC in addition to having abnormalities along two of the following variables: glucose regulation, dyslipidaemia, and blood pressure.	NW OW	P		P (VAT)		-SCD16: significantly positively associated with BMI and VAT. -The observed association between SCD16 and VAT was dependent on BMI. -SCD18: negatively associated, but not significantly. -PA and PAL: significantly positively associated with BMI. -Overweight subjects defined as having and not having the MetS did not have significant differences with regard to BMI, WC, VAT nor SCD16 and SCD18 indices. -Similar associations between metabolic health irrespective of anthropometric and SCD-1 indices were seen among normal weight participants.
30. Relationship between the estimates of desaturase activities and cardiometabolic phenotypes in Koreans, Do, Chung, Moon & Shin, 2011.		NW OW	P				-SCD16 was significantly positively associated with BMI, but the positive association with WC did not reach significance. - SCD18 was negatively associated, but not significantly. -PAL was significantly positively associated with BMI, but not with WC.
31. Serum Fatty Acids, Desaturase Activities and Abdominal Obesity – A Population-Based Study		OW	Not invest igate.	P (WC)	P (WHR) and (SAD)		-The estimated SCD16 index was associated with abdominal obesity (WC, WHR and VAT). - In multivariate logistic analysis they observed that the adjusted OR for finding

of 60-Year Old Men and Women, Alsharari et al., 2016							an increased proportion of abdominal fat tissue was a difference of 4.06 from 3.27 in the lowest percentile to 5.05 in highest percentile of estimated SCD16 (in a score calculated from measured PA and estimated SCD16 and D6D activity).
32. Fatty acid metabolism is altered in non-alcoholic steatohepatitis independent of obesity, Walle et al., 2016	<u>KOBS-study:</u> - All subjects were scheduled for gastric bypass operation. Some participants had diabetes. -Followed a preoperative special menu designed for a VLCD with a daily energy intake of 600–800 kcal. -Subjects were analysed according to the extent of liver fat build up and divided into three groups with increasing severity: 1.Normal liver, 2.Steatosis and 3.Steatohepatitis (NASH) -Liver fat was determined by histology - Liver FA composition (determined by histology) and SCD16 activity estimates were determined based on circulating serum lipids and liver FA composition.	Kobs: MOB Metsim: NW OW	KOBS: Not investigated. METSIM: P			KOBS: P (liver) METSIM: P (liver)	<u>KOBS-study:</u> SCD16: Significantly positively associated with LF in CE and PL, but not TGR. -No statistical analysis investigating the relationship between SCD16 activity estimates and BMI was included. -Since the spread of data around mean BMI was quite high, BMI may potentially have been associated with SCD16 estimates. <u>METSIM-study:</u> -The low LF group had significantly lower BMI and WC than the high LF group. -The high LF group also had significantly higher SCD16 indices. - SCD16 was significantly positively associated with LF.

	<u>METSIM-study:</u> -A previously published NASH score as well as circulating serum ALT was used as an indicator to estimate excess liver fat.						
33. Palmitoleic acid is elevated in fatty liver disease and reflects hepatic lipogenesis, Lee et al., 2015	-FA composition was measured in plasma VLDL TGR and plasma FFA and SCD-1 and DNL estimated from data on isotopically determined DNL and liver fat. -Received a weight-maintaining menu (based on the participant's normal diet) to be followed for 10 days before blood test. -The subjects were periodically re-examined for three years.	OW OB	Not investigated.			P (liver)	-SCD16 and PAL (but not FFAs) were significantly positively associated with isotopically determined LF. -SCD16 and PAL measured in VLDL-TGR (as well as FFAs) were significantly positively associated with isotopically determined DNL. -SCD18 estimated in VLDL-TG or FFAs were not associated with LF, but FFA estimates were significantly positively associated with isotopically determined DNL. -They conclude that their data provided support for the use of PAL estimated in VLDL-TGR as a biomarker for elevated liver fat when isotope use is not feasible.
34. Serum fatty acid composition and insulin resistance are independently associated with liver fat markers in elderly men, Petersson et al., 2010		NW OW	Not investigated			P (liver)	- SCD16: Significantly positively associated with LF (measured by ALT). -Significant positive relationship between SCD16 and WC, but the association disappeared after being controlled for LF. -When they adjusted the association between SCD16 and LF for BMI, the positive

							relationship between SCD16 and liver fat remained virtually unaffected. -The independent relationship between SCD16 and LF remained also after insulin resistance had been controlled for.
35. Fatty acid composition in serum cholesterol esters and phospholipids is linked to visceral and subcutaneous adipose tissue content in elderly individuals: a cross-sectional study, Rosqvist et al., 2017	-The amount of visceral and subcutaneous abdominal AT was measured by MRI. -Liver fat by spectroscopy. -BF and trunk fat by dual-energy X-ray absorptiometry (DXA).	OW	P?	P (Adominal SAT)			- SCD16: A possible association with BMI was not investigated. -SCD16: significantly positively associated with abdominal SAT, FM and trunk fat, but SCD16 was not with associated with VAT.
36. High Hepatic SCD1 Activity Is Associated with Low Liver Fat Content in Healthy Subjects under a Lipogenic Diet, Silbernagel et al., 2012.	Between baseline and follow-up: -Monosaccharides (600 kcal) added to a balanced diet for 4 weeks. -Consumed three times daily; not specified whether taken together with or separately of mealtime.	OW	Not investigated.			N (liver)	Baseline: - SCD16: not associated with LF at baseline and negatively associated with the change in LF between baseline and follow-up after four weeks on an excess energy diet.
37. Low hepatic stearoyl-CoA desaturase 1 activity is associated with fatty liver and insulin resistance in	-They recruited participants with a BMI at or above 27 kg/m2. -Subjects were analysed according to body fat percentage: lean (body fat	OW OB MOB	Not investigated.			N* (liver)	-SCD18: not associated with BF and VAT. - When adjusted for age and BF, liver fat was negatively associated with SCD18 among participants classified as obese according to BF% whereas no associations

obese humans, Stefan et al., 2008	26.5 ± 1%) and obese (body fat 35.6 ± 1%) -Nine-month long intervention period with counselling for a healthier diet and physical activity. -Goal: 5% weight reduction						were observed among participants classified as lean. -The life-style intervention resulted in significant decreases in BMI, VF and LF. -Among subjects classified as obese at baseline according to BF%, a high SCD18 at baseline predicted a reduction in LF when moving from baseline to follow-up. The same association was not observed among individuals classified as lean according to BF%.

Legend:

Added * reflects SCD18

P – Positive association

N – Negative association

WC, WHR and WtHR: indicators of body fat distribution and abdominal fat (Piqueras, 2017).

VAT, WHR and SAD: indicators of visceral fat (Piqueras, 2017).

a – Boys/men

b – Girls/women

1-Baseline

2-Follow-up

Table IV

General characteristics of the study population, applied lipid fractions and findings regarding possible associations in the included studies.

Title	Author, country and Journal	Number of subjects, gender and age. Study design	BMI Other adiposity indicators and measures	SCD-1 activity (SCD16 and SCD18) Lipid fraction for SCD-1 estimation
1. Associations Among Fatty Acids, Desaturase and Elongase, and Insulin Resistance in Children	Beccarelli et al., 2018. *Journal of the American College of Nutrition*, USA.	n=86 33 boys and 53 girls Age: 9-12 Cross-sectional study.	<u>BMI for age percentile</u> Normal weight 17.3 +/-1.3, Overweight 21.0 +/-0.9 Obese 26.2 +/-3.1 <u>WC</u> Normal weight 66.1 (+/- 8.7), Overweight 62.5 (+/- 10.2), Obese 79.5 (+/- 15.4)	SCD16: No significant association with BMI SCD18: No significant association with BMI. Fasting plasma total lipids.
2. Association of Plasma Lipids Fatty Acid Composition with Metabolic Profile of Czech Adolescents	Hlavaty et al., 2015. *Physiological Research*, Czech Republic	n=380, Girls and boys. Age: 16.4 +/-0.9 Cross-sectional study. Plasma total lipids.	BMI 22.3 (+/-4.0) Participants were categorised as: -Normal weight (BMI between the 25th and 75th percentile) -Overweight (BMI between the 25th and 75th percentile)	SCD16: No association with BMI. SCD18: No association with BMI. SCD16: Significant positive association with percentage body fat. SCD18: No significant associations, but a negative direction

			-Obese (BMI above the 95th percentile. WC 80.6 (+/- 10.2)	-Palmitoleic acid: Significant positive association with percentage body fat across all three lipid fractions, and with BMI in PLs and CEs.
3. Plasma palmitoleic acid content and obesity in children	Okada et al., 2005. *The American Journal of Clinical Nutrition*. Japan.	<u>Obese</u> n=59 39 boys and 20 girls Age: 11.8 (± 3.8) <u>Non-obese</u> n = 25 Gender: 25 M, 28 F Age: 12.6 (± 0.5) Case-control study.	<u>Obese</u> BMI: 29.5 (±4.92) Relative body weight (%): 158.3 (± 23.5) WC: 89.2 ± 12.1 Waist-hip ratio: 0.92 ± 0.07 Percentage body fat: 33.2 ± 7.82 <u>Non-obese</u> BMI: 17.9 ± 1.7 Relative body weight (%): 95.7 ± 9.1 WC: Not detectable Waist-hip ratio: Not detectable Percentage body fat: 19.8 ± 4.6	-SCD16: Significantly positively associated with BMI. -SCD16: Significantly positively associated with WHR. -SCD16: Not significantly associated with percentage body fat. -Plasma PAL was significantly positively associated with WC, WHR and WHtR, but not with BMI and RW in obese children. Plasma total lipids.
4. Associations Between Estimated Desaturase Activity and Insulin Resistance in Korean Boys	Choi et al., 2014. *Public Health and Research Perspectives*. Korea	n=131 Boys Age Baseline 9 Follow-up 11	<u>Baseline</u> -Lean (n = 56): BMI: 18.2 ± 0.5 WC: 62.4 ± 3.7 -Obese (n = 75): BMI: 23.8 ± 2.3 WC: 77.6 ± 6.2 <u>Follow-up</u>	Baseline: SCD-16: Significantly positively associated with BMI, WC and the metabolic risk score. Follow-up: -SCD16: Positively, but not significantly, associated with BMI and WC.

		Prospective longitudinal study, two years. Plasma phospholipids	-Lean (n = 40): BMI: 18.8 ± 0.8 WC: 66.4 ± 5.1 -Intermediate (n = 34): BMI 21.7 ± 1.0 WC 74.9 ± 5.8 -Obese (n = 57): BMI: 26.2 ± 3 WC: 85.5 ± 8.1	-SCD16 was equally high between overweight and obese boys, and they had significantly higher SCD16 the compared to the lean boys. -The metabolic risk score was significantly positively associated among obese boys, but inversely associated among the overweight and lean. -SCD-18: No significant associations, but a negative direction of the relationship with BMI, WC and the metabolic risk score.
5. Association of Changes in Body Fatness and Fatty Acid Composition of Plasma Phospholipids during early Puberty in Japanese Children	Abe et al., 2012 *Journal of Atherosclerosis and Thrombosis,* Japan	n=77 Baseline: Age: 9.6 (±0.5) Non-obese 34 boys/32 girls Obese 4 boys and 6 girls Follow-up: Age:12.5 (±0.5) Obese 6 boys and 8 girls Prospective longitudinal study, three years. Plasma phospholipids	BMI was not given. <u>Baseline:</u> RW Boys Non-obese: 102,8(±12,4) Obese: 145,4(±31,8) RW Girls Non-obese: 101,1±11,9 Obese: 139,4,4±13,7 WHtR Boys Non-obese: 0,44±12,4 Obese: 0,58±0.07 WHtR Girls Non-obese: 0,44±0.03 Obese: 0.54±0.05 <u>Follow-up:</u> RW Boys Non-obese: 93.7±8.5	Baseline and follow-up: -SCD16: Not association with neither RW nor WHtR. Baseline: -SCD18: Significantly negatively associated with RW and WHtR among boys, but not girls. Follow-up: -SCD 18: No significant association.

			Obese:131.7±22.6 RW Girls Non-obese: 98.0±12,1 Obese:134.1(±15.3) WHtR Boys Non-obese: 0.41±0.03 Obese: 0.56±0.06 WHtR Girls Non-obese: 0.42±0.03 Obese: 0.51±0.04	
6. Changes in SCD gene DNA methylation after bariatric surgery in morbidly obese patients are associated with free fatty acids	Morcillo et al., 2017. *Science Reports*, Spain	n=120, 30.2%M/69.8%F Age: 43.2 (± 9.4) n=30 Controls 32.1%M/67.9%F Age: 47.2 ± 5.8 Intervention in the study group: Bariatric surgery and standardised VLCD Case-control study.	<u>BMI</u> Study group before/after RYGB: 50.9 (± 7.1)/35.1 (± 6.6) Control group: 33.6 (± 2.3) <u>WC</u> Study group before/after RYGB: 137.3 (± 16.42)/108.8 (± 13.1) Control group: 110.8 ± 8.1	-SCD16 and SCD18: Significantly positively associated with BMI. -SCD16 and SCD18 were significantly associated with weight loss among the participants who lost weight above the 75th percentile. Fasted serum PLs and FFAs.
7. Association between increased visceral fat area and alterations in	Kang et al., 2017 Lipids in Health and Disease, Korea	n=232 T1: 77 T2:78 T3:77 68(M)/164(F)	BMI Low VAT: 26.8 (±0.17) Medium VAT: 26.7 (±0.16) Large VAT: 27.3 (±0.16)	-BMI was not investigated - SCD16 and SCD18: Significantly positively associated with VAT. -The association between SCD16 and VAT was only significant when comparing low and high

plasma fatty acid profile in overweight subjects: a cross-sectional study		Age: 40.2 (±0.68) Cross-sectional study Plasma total lipids	WC Low VAT: 89.2 (±0.67) Medium VAT: 91.5 (±0.60) Large VAT: 92.9 (±0.58) VAT Low VAT: < 71.8 cm2 Medium VAT: ≤ 71.8 cm2 - 99.6 cm2 Large VAT: > 99.6 cm2	VAT, and not when comparing medium and high VAT.
8. Desaturase Activity Is Associated With Weight Status and Metabolic Risk Markers in Young Children	Wolters et al., 2015 *European Journal of Paediatrics*, Germany	Cross sectional (baseline): n=2294 50 % M/W Age: 2.1–9.7 years Follow-up: n=1510 50 % M/W Age: 3.9–11.7 Longitudinal prospective (two years) Whole blood fatty acids Prospective longitudinal study	BMI Cross-sectional Thin: 146 (6.4%) Normal: 1148 (50.0%) Overweight: 536 (23.4%) Obese: 464 (20.2%) Longitudinal analysis Thin: 102 (6.8%) Normal: 763 (50.5%) Overweight: 344 (22.8%) Obese: 301 (19.9%)	-SCD16: Significant positive association with BMI at baseline and follow-up. -Baseline SCD16 had no significant predictive power on BMI at follow-up two years later.

9. Serum phospholipid and cholesteryl ester fatty acids and estimated desaturase activities are related to overweight and cardiovascular risk factors in adolescents	Steffen et al., 2008 *International Journal of Obesity*, USA, Norway, Sweden.	n=164 42W/58M Age 15±1.2 years Cross-sectional study.	BMI Normal weight 20.5 Overweight 28.2 WC: 73.2/90.8 Serum CE and PL.	- SCD16: Significantly positively associated with BMI in CE estimates, but not significant in PL. - SCD16 in significantly positively associated with WC in CE estimates, but not PL. - The significant relationship of SCD16 with BMI and WC was lost in multiple regression analysis together with other cardiovascular risk factors.
10. Effects of two-months balanced diet in metabolically healthy obesity: lipid correlations with gender and BMI-related differences	Rondanelli et al., 2015 *Lipids in Health and Disease*, Italy.	n=103 MHO subjects (30/73 M/F; age:42.2 ± 9.5) Prospective longitudinal study with intervention.	BMI 30.2 ± 3.2 -Overweight (BMI < 30): 55 -Obese (BMI > 30): 48 Serum phospholipids and cholesterol esters	-This was a metabolically HEALTHY population - SCD18 activity estimates were significantly negatively associated with BMI. SCD16 was not associated. -SCD16 and SCD18 were significantly lower among females than men. -An intervention with energy reduction and nutritional improvement resulted in significant reductions in BMI and android fat mass, but no changes in neither SCD16 nor SCD18 activity estimates. -Results were similar for men and women and participants with higher and lower BMI.
11. Docosahexaenoic Acid Content in Plasma	Saito et al., 2011 *Journal of Atherosclerosis*	n=32 27M/5F Age: 12.0 (±2.6) years	BMI 29.1 +/-5.0 (M)/29.0 +/-5.9 (F)	-Both SCD16 and SCD18 were significantly positively associated with BMI. -SCD16, but not SCD18, was also significantly positively associated with WHtR.

Phospholipids and Desaturase Indices in Obese Children	*and Thrombosis.* Japan.	Cross-sectional study.	Obesity was defined as relative body weight greater than 120% of the standard weight for sex, age and height WHtR 0.60 (+/-0.01) (M)/0.58 (+/-0.04) (F) Plasma phospholipids	-SCD16 was significantly positively associated with insulin and VLDL-TGR whereas SCD18 was only significantly positively associated with TGR synthesis. -DHA content was significantly negatively associated with both SCD16 and SCD18. -Girls had higher SCD16 and SCD18 estimates than boys (however boys were strongly over-represented and only five girls had been recruited (as opposed to 32 boys).
12. Relationship between estimated fatty acid desaturase activities and abdominal adiposity in Japanese children	Saito et al., 2014. *Obesity Research & Clinical Practice*. Japan	n=181 (98M/83 F) Age: 11.0 Case-control study.	<u>Percentage overweight (POW):</u> -Without abdominal obesity: 1.5 ± 10.6 (M)/-0.0 ± 12.7 (W) -With abdominal obesity: 44.1 ± 18.1 (M)/46.1 ± 19.6 (W) <u>Overweight (%):</u> -With abdominal obesity 46.1 ± 19.6(F)/44.1 ± 18.1 (B) -Without abdominal obesity: -0.0 ± 12.7(F)/1.5 ± 10.6 (B)	-POW was significantly higher among children with abdominal obesity. -In total subjects combined, WHtR was significantly negatively associated with SCD18 activity estimates. -When the analysis was made within the groups with low and high WHtR respectively, it was observed that among the children without abdominal obesity SCD18 was negatively associated whereas it was positively associated among children with abdominal obesity. -The children with abdominal obesity had both significantly higher WHtR as well as significantly higher POW. Fasting plasma phospholipids Case-control study
13. Fatty Acid Composition of	Zeman et al., 2017	<u>Study group</u> n=300 (152M/148F) Age 47 (40-55)	<u>Study group</u> BMI 27.9 (25.4-30.9) WC 96 (88-105)	-The overweight study group with metabolic syndrome related traits had significantly higher

Plasma Phosphatidylcholine Determines Body Fat Parameters in Subjects with Metabolic Syndrome-Related Traits	*Metabolic Syndrome and Related Disorders*. Czech Republic.	<u>Healthy controls</u> n= 70 (36M/34W) Age 43 (33.2-54.8) Case-control study.	WHR 0.9 (0.9-1) <u>Healthy controls</u> BMI 23.2 (21.3-25.1) WC 78 (75-86.5) WHR 0.8 (0.8-0.9) Plasma PL phosphatidyl choline	SCD16 activity estimates as well as measured PAL and SA than the healthy normal weight. -The metabolic syndrome group had significantly higher BMI, WC, WHR, body fat percentage and total fat mass. -No statistical analysis investigating a possible association between BMI and FA composition and SCD16 activity indices was included, so it is unknown the extent to which the difference in SCD16 activity was related to BMI or some of the other metabolic indicators differentiating the participants with and without metabolic syndrome related traits. SCD18 was not significantly different in the high or low TG group. We do not know the extent to which it was associated with WC or BMI. -PAL and SA were significantly positively associated with WC in the study group. -In the study group with the metabolic syndrome Zeman et al. found that 1. male gender contributed to higher values of WC and WHR. In contrast, body fat and body fat percentage were negatively associated with male gender and that 2. Age was positively associated with WHR among the males and fat percentage among the women in the study group only.
14. Association between serum	Aglago et al, 2017.	n= 372 women Age: 50.1 (± 9.5)	BMI 30.3 +/- 5.2 WHR	-SCD16 was significantly positively associated with BMI and WC, but the association with WHR did not reach significance.

phospholipid fatty acid levels and adiposity in Mexican women	*Journal of Lipid Research.* France and Mexico	Randomly selected participants recruited from a group of controls that had taken part in a population-based case-control study on breast cancer. Cross-sectional study.	0.91 ± 0.06	-SCD18 was significantly negatively associated with BMI and WC, but significance was lost when tested for false discovery rate (false positives). -SCD18 was not associated with WHR. -SCD-16 was significantly associated to most of the FAs associated with BMI, WC, and WHR. -PAL was significantly positively associated with BMI and WC, but not with WHR. OA was not significantly associated. -BMI categories for underweight, normal or healthy weight, overweight, obesity, and morbid obesity were respectively <18.5 kg/m2, 18.5–24.9 kg/m2, 25–29.9 kg/m2, 30–39.9 kg/m2, and from and above 40 kg/m2. The exact distribution in each category was not given, but the prevalence of overweight and obesity was 43.0% and 45.7% with a mean BMI of 30.3 kg/m2. Serum phospholipids
15. Comparison of dietary and plasma phospholipid fatty acids between normal weight and overweight black South Africans according to metabolic health:	Ojwang et al., 2020. *Prostaglandins, Leukotrienes, and Plasma Phospholipids Fatty Acids*. South Africa.	n = 711: 345 MHNW 79 MUNW 120 MHO 167 MUO Age: 51 MHNW 51 MUNW 49 MHO 55MUO	<u>BMI</u> 19.8 (17.8-22.0) MHNW 21.4 (19.1-23.3) MUNW 30.4 (26.9-34.1) MHO 31 (27.6-34.5) MUO <u>WC</u> 71.7 (66.5-76.0) MHNW 78.4 (69.5-83.5) MUNW 89.5 (82.3-94.9) MHO	Within BMI groups: -SCD16 and SCD18 were positively associated with BMI and negatively with metabolic health Between BMI groups: - SCD16 and SCD18 were negatively associated with BMI -Women and men from rural and urban areas. Plasma phospholipids

The PURE study.		Black South Africans only. Cross-sectional study.	92.6 (86-99.5) MUO	
16. Plasma lipid fatty acid composition, desaturase activities and insulin sensitivity in Amerindian women	Vessby et al., 2012. *Nutrition, Metabolism and Cardiovascular Diseases*. Sweden and Peru.	Gender: women only Shuar women: n=59, 35,7 years (+/-12) Lima women: n = 141, 40 years (+/- 11,1) Swedish women: n= 295 (40,6 (+/- 9,9) Cross-sectional study.	BMI Shuar women: 23.6 (+/-2.7) Lima women: 25.9 (+/-4.9) Swedish women: 23.7 (+/-3.8)	-SCD16 was significantly positively associated with BMI among the three groups of women -SCD16 was significantly positively associated with body fat among the women from Lima and positively associated among the women from the Shuar region (but not significantly). No data on the women from Sweden. -The women from Lima had significantly higher body fat percentage compared to the Shuar women as well as higher (but not significantly) BMI. -The women from Lima had significantly lower PA, PAL, OA and SCD16 compared to the women from the Shuar region, but interestingly – SA was similar (possibly reflecting a indicating healthy, fully functioning SCD-1 enzyme desaturation capacity among the Shuar women).
17. Serum Phospholipid Fatty Acids Levels, Anthropometric Variables and Adiposity in Spanish Premenopausal Women	Del Pilar del Pozo et al., 2020. *Nutrients*, Spain.	n=1443 Age: 44.3 (2.8) Females only Cross-sectional study	<u>BMI</u> 24.3 (+/- 4.3) <u>WC</u> 80.0 (+/-11.2) <u>Body fat percentage</u> 30.3 (+/-7.3) <u>Waist-to-hip ratio</u> 0.8 (+/-0.1)	-SCD16 was significantly positively associated with BMI and withstood testing for adjustment factors and false discovery rate. - SCD16 was not associated with WC, VAT and BF% when tested for adjustment factors and false discovery rate.

		Serum phospholipid fatty acids.	<u>Visceral fat index</u> 5.2 (+/-2.4)	-SCD18 was significantly negatively associated with BMI, and significantly positively associated with WC. -PAL was significantly positively and OA significantly negatively associated with BMI.
18. Effect of weight loss on circulating fatty acid profiles in overweight subjects with high visceral fat area: a 12-week randomized controlled trial	Lee et al., 2018, *Nutrition journal*. Korea	-12-week, placebo-controlled, randomized study. n=75 Weight-maintenance group (n = 38) Age 46.0 ± 1.35 Male/female 11 (28.9)/27 (71.1) Weight-loss group (n = 37) Age 44.1 ± 1.92 Male/female 15 (40.5)/22 (59.5) Case-control study with intervention and prospective longitudinal data.	<u>BMI:</u> -Weight-maintenance group: Baseline: 27.3 +/-0.25 Follow-up: 27.4 +/- 0.24 (change 0.17 (0.04) -Weight loss group: Baseline: 27.3 +/- 0.23 Follow-up: 26.4 +/- 0.24 (change -0.90 (+/-0.08). <u>WC:</u> -Weight-maintenance group: Baseline: 93.6 (+/- 0.82) Follow-up: 94.4 (+/- 0.83) (change 0.13 (+/- 0.21) -Weight-loss group: Baseline: 93.0 +/- 0.86 Follow-up: 91.5 (+/- 0.80) (change - 1.48 (+/- 0.31) They recruited participants with a VAT at L4 at or above 100 cm2.	-SCD18 was not associated. -The weight loss group had significantly larger reductions in SCD16 and PAL than the weight maintenance group. Accordingly, SCD16 and PAL were potentially significantly positively associated with treatment, i.e., reductions in energy intake and changes in dietary composition. -Treatment resulted in reductions in BMI and other anthropometric indicators as well as changes in SCD16 indices and FA composition (PA, PAL, SA and OA were significantly reduced between baseline and follow-up in the intervention group). -The decrease VAT was significantly positively associated with reductions in weight, BMI, WC, FM% and FM as well as insulin regulation, but not with SCD16. - We do not know the extent to which it was the energy reduction and/or dietary changes that had resulted in the significant reductions in BMI and changes in body composition and the changes in FA composition and reductions in SCD16 activity.

19. Plasma palmitoleic acid, a product of stearoyl-coA desaturase activity, is an independent marker of triglyceridemia and abdominal adiposity	Paillard et al., 2008. *Nutrition, Metabolism and Cardiovascular diseases*. France.	The study population was analysed according to plasma triglyceride percentiles: Below 75th n = 101 Age: 41 At or above 75th percentile n = 33 Age: 41 Men only Cross-sectional study.	Below 75th BMI 24.1 (3.0) WC: 84.8 (9.0) At or above 75th percentile BMI 26.2 (3.4) WC: 93.5 (10.0) Plasma total FAs	-SCD16 was significantly increased in the high TG group who also had a significantly higher BMI and significantly wider WC than the low TG group. -SCD-1 enzyme activity was not included in the multivariate model testing independent correlations with WC. PAL was significantly positively associated with WC before but not after adding TGs among the independent variables. -Paillard concluded that TG was independently associated with both PAL and WC. -SCD18 was not significantly different in the high or low TG group. We do not know the extent to which it was associated with WC or BMI.
20. Fatty acid profile and estimated desaturase activities in whole blood are associated with metabolic health	Svendsen et al., 2020. *Europe PMC.* Norway.	n=321 individuals <u>Normal weight</u> MH - (n=64) MU (n=11) <u>Overweight</u> MH - (n=52) MU (n=23) <u>Obese</u>	<u>Normal weight</u> MH 22.7 (+/- 1.5)/MU 23.9 (+/-0.8) <u>Overweight</u> MH - 27.1 ± 1.3 /MU 27.2 (±1.4) <u>Obese</u> MH 33.3 (± 3.4) /MU 33.8 (± 3.6)	An independent association between SCD16 and SCD18 with metabolic health was observed irrespectively of BMI: -SCD16 and SCD18 increased with increasing criteria of MU in all three BMI categories and decreased with decreasing criteria of MU. -Differences in SCD16 and SCD18 activities between the MH and MU were similar within each BMI category when comparing MU and MH

		MH (n=34) MU (n=18) Cross-sectional study.	Whole blood	subjects, and the distribution in the number of participants with MU and MH in each category of BMI was similar. -The definition of metabolic health did not include any anthropometric indicators. -No information on WC nor VAT was given. -Whole blood
21. Associated factors of estimated desaturase activity in the EPIC-Potsdam study	Schiller et al, 2014. *Nutrition, Metabolism and Cardiovascular Diseases*. Germany.	n = 1782 Total age: 35–65 Age quintiles based on SCD16 estimates: Q1 49.68 (±8.99)/ Q5 52.31 (±8.55) Cross-sectional study.	Average BMI: 27. <u>BMI</u> quintiles according to SCD16 activity estimates: Q1: 25,21 (±3.80)/Q5: 27.09 (±4.34)	BMI and WHR were positively associated with SCD16, but explained only small proportion of variance in enzymatic activity: BMI: 0.70% and WHR: 0.96% <u>Extreme quintiles of SCD16 activity:</u> Q1: 0,013 – Q5: 0,030 (median) Q1: 0.004-0.015 -Q5: 0.026-0.0860 (range) Erythrocyte membrane phospholipids
22. Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men.	Warensjø et al, 2005. *Diabetologia*. Sweden.	n=1360 (baseline) n=706 (follow up) Men only Age 50 at baseline and 70 at follow-up. Population-based prospective cohort study.	Baseline characteristics of the men who…: 1. …<u>did</u> develop the metabolic syndrome: BMI: 25.6 (±2.5) WC: 88.2 (±7.2) 2. …<u>did not</u> develop the metabolic syndrome: BMI: 23.9 (±2.4) WC: 84.4 (±6.7)	-A high SCD16 index was associated with increased BMI 20 years later. -A high SCD16 also predicted having the metabolic syndrome, but the increased risk of developing the metabolic syndrome 20 years later was dependent on BMI and physical activity. Secondary to BMI also WC had an influence on the relationship. -Anthropometric and all metabolic indicators -Logistic regression analysis established that the risk of developing the metabolic syndrome between baseline and follow-up increased by 30% for each SD increase of SCD16.

			-Evaluated at age 50 (baseline) and reinvestigated 20 years later (follow-up).	-SCD18 did not have predictive value. -The relative amounts of several SCD-1 related FAs were significantly higher among those who developed the metabolic syndrome (MA, PA, PAL and OA, but not SA). They concluded that serum FA composition may predict the long-term development of the metabolic syndrome. -In addition to the potential influence of endogenous process on the development of the metabolic syndrome, Warensjø et al. stressed diet, genetic build-up, hormones and lifestyle factors like physical exercise. - At the age of 70 16.9% additional participants had developed the metabolic syndrome since baseline, reaching a prevalence of 19.8% in the entire population. Serum cholesteryl esters (CEs)
23. Fatty acid composition and estimated desaturase activities are associated with obesity and lifestyle variables in men and women	Warensjø et al., 2006. *Nutrition, Metabolism and Cardiovascular Diseases*. Sweden.	n=849 Gender: Men 554/women 295 Age: Men - 40.6 (9.1) Women - 40.6 (9.9) Cross-sectional study	BMI Men 24.7 (±3.2)/Women 23.7 (±3.8) WC 88 (±8.6)/79 (±9.0) SAD (VAT)	-Strong and positive associations between SCD16 and indicators of obesity (BMI, SAD and WC). -The associations were independent of confounding from age, physical activity, and total intake of fat (E%). -In bivariate analysis in the total population, the significant association between VAT and SCD16 was lost when adjusted for BMI, but remained significantly associated among men.

			Serum cholesteryl esters	-In logistic regression analysis SCD16 was found to have a significant ability to predict BMI. The risk of being overweight increased with 50–60% for each standard deviation increase in SCD16, and the predictive value remained after being controlled for physical activity and total fat intake (E%). -SCD18 was not related to being overweight. -Women had significantly higher levels of SCD16 and SCD18 than men.
24. Associations between estimated fatty acid desaturase activities in serum lipids and adipose tissue in humans: links to obesity and insulin resistance	Warensjø et al., 2009 *Lipids in Health and Disease*. Sweden.	n=301 Age: 63 (0.7) Men only Cross-sectional study.	BMI 25.9 (±3.1) Serum phospholipids and serum FFA (as well adipose tissue triacylglycerols)	-SCD16 estimates in PLs were significantly positively associated with BMI while SCD18 estimates were significantly negatively associated. - SCD16 estimates in FFA were positively associated with BMI, but not significantly. -SCD18 estimates in FFA and AT- TAG were significantly positively associated with BMI. - Insulin-resistant subjects had significantly higher adipose tissue SCD-18, compared to insulin-sensitive subjects. SCD18 estimates in AT-TGR were significantly positively associated with insulin resistance. High SCD16 in AT-TGR was not associated.
25. Plasma stearoyl-CoA desaturase indices: Association with lifestyle, diet,	Vinknes et al., 2012. *Obesity*. Norway.	n=2021 (924M/1097W) Age: 71-74 Plasma total FAs	BMI 26 (M) (62,6 % overweight/8,7 % obese) 26,1(W)	-Plasma SCD16 and SCD18 indices were significantly positively associated with BMI and BF% (adjusted for gender and lean body mass). -The OR for high BF% and elevated BMI increased significantly with higher quintiles of plasma SCD-1 indices.

and body composition		Cross-sectional study.	(58,8 % overweight/16.7 % obese)	-Results remained similar after adjustment for lifestyle and dietary factors. -No gender-related differences were observed.
26. Fatty Acid Profile and Desaturase Activities in 7–10-Year-Old Children Attending Primary School in Verona South District: Association between Palmitoleic Acid, SCD-16, Indices of Adiposity, and Blood Pressure	Bonafini et al., 2020. *International Journal of molecular sciences*. Italy.	n=243 children Age: Excess weight 8.6 (± 0.7) Normal weight 8.69 (± 0.72) Caucasian: 163 Non-Caucasian: 80 Cross-sectional study.	<u>BMI</u> Excess weight (n=88) 21.7 (± 2.8) Normal weight (n=155) 16.3 (± 1.7) Caucasian (n=163) 18.1 (± 3.45) Non-Caucasian (n=80) 18.4 (± 3.33) Excess weight = BMI for age above the 85th percentile (overweight + obese (above the 95th)	-BMI, WtHR and FM were significantly positively associated with SCD16, but WtHR and FM lost significance when BMI was added to the model. -BMI and FM were negatively associated with SCD18, but significance was lost when controlled for false discovery rate. -In logistic regression analysis the children in the fourth quartile of SCD16 had a six-times-higher OR of being OW or OB compared to the first quartile. Whole-blood
27. Association between Serum Phospholipid Fatty Acid Levels and Adiposity among Lebanese Adults: A Cross-Sectional Study	Yammine et al., 2018. *Nutrients*, Lebanon.	n=395 Men: 129/women 266 Age: 44.5 ± 15.3 (mean)/38.8 ±16.3(M) 47.3±14.0(W) Cross-sectional study.	<u>BMI</u> Men: Underweight and normal (<25): 32.6% Overweight (25–29.99): 37.2% Obese (≥30): 30.2% Women: Underweight and normal (<25): 22.9% Overweight (25–29.99): 31.6% Obese (≥30 kg): 45.5%	-Significant associations between SCD16 and SCD18 and the anthropometric indicators BMI and WC were only seen among women. -SA and PAL were significantly positively, and OA significantly negatively, associated with BMI among women. -Among women SCD16 was significantly positively associated with BMI and WC, but lost significance when tested for false discovery rate. -Among women SCD18 was significantly negatively associated with both BMI and WC. The association withstood testing for false discovery.

				-Men had significantly lower BMI and BF%, but significantly larger WC.
28. Fatty Acid Profile of Mature Red Blood Cell Membranes and Dietary Intake as a New Approach to Characterize Children with Overweight and Obesity	Jauregibeitia et al., 2020 *Nutrients*, Spain.	Age: 6 – 16 years old n = 209 For SCD aktivitet bruk tall i tabell tre. Case-control study	Normal weight (NO) n = 107 Overweight (OV) n = 41 Obese (OB) n = 61 Red blood cell membranes phospholipids	-The SCD16 index did not differ between NW, OW and OB children. -The SCD18 index was significantly negatively associated with BMI. The NW had significantly higher SCD18 activity estimates than the overweight and obese.
29. Visceral fat thickness in overweight men correlates with alterations in serum fatty acid composition	Tomonori Kishino et al., 2008. *Clinica Chimica Acta*, Japan	n=45 Men only Normal weight (n=21) Age 62 (±13) Overweight (n=25) Age 56 (±13) Serum total lipids Cross-sectional study	BMI Normal weight 22 (+/- 1,9) Overweight 27 (+/-2.7) VAT Normal weight 36 (+/- 12) Overweight 62 (+/-21)	-SCD16 was significantly positively associated with BMI and VAT, and remained significant after adjustment. SCD18 was negatively associated, but not significantly. -The observed association with VAT was dependent on BMI -PA and PAL were significantly positively associated. -Both NW and OW subjects defined as having and not having the metabolic syndrome did not have significant differences with regard to BMI, WC, VAT nor SCD16 and SCD18 indices.

30. Relationship between the estimates of desaturase activities and cardiometabolic phenotypes in Koreans	Do, Chung, Moon & Shin, 2011. *Journal of Clinical Biochemistry and Nutrition*. Korea.	n=93 36 men and 57 females Age= 54.4 ± 13.4 Cross-sectional study	BMI = 23.3 ± 2.7	-SCD16 was significantly positively associated with BMI, but the positive association with WC did not reach significance. -SCD18 was negatively associated, but not significantly. -PAL was significantly positively associated with BMI, but not with WC.
31. Serum Fatty Acids, Desaturase Activities and Abdominal Obesity – A Population-Based Study of 60-Year Old Men and Women	Alsharari et al., 2017. *PloS one*, Sweden.	n =3898 Men (n = 1883) Females (n = 2015) 60-year old BMI: 26.6 (M)/25.9 (W) WC: 97.8 (M)/ 86.4 (W) Cross-sectional study.	Serum cholesteryl esters	-Women had significantly higher SCD16 than men despite having significantly lower BMI, WC, SAD, WHR and WtHR. -A significant and linear association was found between SCD16 estimates and indicators of abdominal obesity (WC, SAD, WHR), with no significant differences between men and women. -In logistic regression analyses the OR for observing abdominal obesity increased by 4.06 when comparing the highest versus the lowest quartile of SCD16. -Women had significantly lower serum PA, but a higher SCD16 index. They also had lower fasting insulin.
32. Fatty acid metabolism is altered in non-alcoholic steatohepatitis	Walle et al., 2016. *Metabolism*, Finland.	Kuopio Obesity Surgery Study (KOBS-study) n = 92 30M/62W age 46.8 ± 9.5	BMI Normal liver 43.7 ± 6.9 Steatosis 44.5 ± 4.6 Steatohepatitis 44.7 ± 6.3	-Significant positive association between SCD16 and liver fat. -They argued that observed differences in SCD16 estimates and fat had been controlled for confounding due to a standardized pre-surgery VLCD diet and the equal BMI.

independent of obesity.		Case-control study, cross sectional data Data included for comparison: Metabolic Syndrome in Men (METSIM study) n = 769 Age 47-75 years Men only	(Liver fat and SCD gene expression were determined by liver histology). <u>Control study</u> BMI Low ALT 25,6 ± 3,0 High ALT 27,6 ± 3,9 (Serum alanine aminotransferase (ALT) was used as a marker of liver fat). -SCD16 was estimated in serum CE, TG and PL.	-Since the spread of data around mean BMI was high at the same time as both the medium and high liver fat group had somewhat higher BMI (although not significantly) than the low liver fat group, it cannot be excluded that BMI may have had an influence on SCD16 and/or liver fat. <u>Control study</u> -They compared their observations with data from the population based METSIM study. -Among the METSIM participants, they found a significant positive association between SCD16 and liver fat (ALT) in CE, but the high liver fat group also had significantly higher BMI. The relative influence of BMI on SCD16 and liver fat is unknown, but the high liver fat group also had with significantly higher BMI also had a significantly higher liver fat score, and as such strengthening the possibility for that also/or BMI may have been associated and implicated in the results.
33. Palmitoleic acid is elevated in fatty liver disease and reflects hepatic lipogenesis.	Lee et al., 2015. *The American Journal of Clinical Nutrition*, Korea.	N=24, Age and gender distribution is not given, only that they were matched for age. Men and females included.	BMI High liver fat 35.3 ± 7.7 Low liver fat 34.9 ± 5.2 -Liver fat and de novo lipogenesis (DNLMeas) were isotopically measured using consumed D2O, measured by spectroscopy as well as	-Despite similar BMI participants had large differences in liver fat. -Estimated SCD16 was significantly positively associated with liver fat. -SCD18 was not associated with liver fat. -SCD16 but not SCD18 was significantly associated with DNL.

		Prospective case-control study. LowLF n = 11 HighLF n = 13	estimated from plasma VLDL-TGR and plasma FFAs. -The 18:0 to 16:0 was used as an index of elongase activity (ELOVL6, elongation of very-long-chain fatty acid protein 6)	
34. Serum fatty acid composition and insulin resistance are independently associated with liver fat markers in elderly men	Petersson et al, 2010. *Diabetes Research and Clinical Practice*, Sweden.	Age: 71 (±0.6) n = 546 Men only Cross-sectional study.	BMI 26.3 ± 3.4 ALT in serum was used as a surrogate marker of fatty liver Serum CEs	-Significant positive relationship between estimated SCD16 activity and liver fat (ALT) independently of BMI, WC and insulin resistance.
35. Fatty acid composition in serum cholesterol esters and phospholipids is linked to visceral and subcutaneous adipose tissue content in elderly individuals: a cross-sectional study, Rosqvist et al., 2017	Rosqvist et al., 2017. *Lipids in Health and Disease*, Sweden.	n = 287 48F/52M Age 70 Cross-sectional.	BMI 26.8 ± 4.1 The association between estimated serum SCD16 activity and the size of abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) was investigated. -The amount of SAT and VAT was measured by MRI.	-Serum CE PA was significantly positively associated with the size of VAT, but not abdominal SAT or BF%. -In serum CE and PL, the SCD16 activity index was significantly positively associated with abdominal SAT and BF%, but not VAT.

			-Liver fat was measured by spectroscopy -Total body fat and trunk fat was measured by dual-energy X-ray absorptiometry (DXA). Serum CE and PL.	
36. High Hepatic SCD1 Activity Is Associated with Low Liver Fat Content in Healthy Subjects under a Lipogenic Diet.	Silbernagel, et al., 2012. *The Journal of Clinical Endocrinology & Metabolism*, Germany.	n = 20 (12M/8F) Age 30.5 ± 2.0 Intervention: Monosaccharides (600 kcal) added to a balanced diet for 4 weeks Liver fat content was determined with spectroscopy.	BMI 25.9 ± 0.5 Plasma VLDL TGR DNL estimated by the ratio 16:0/18:2n-6) SCD16 only	-Four weeks on a lipogenic (excess energy) diet resulted in a parallel increase in DNL and SCD16. -SCD16 was not associated with liver fat at baseline and was negatively associated with the increase in liver fat between baseline and follow-up. -Estimated DNL was significantly positively associated with liver fat at baseline and was significantly positively associated with liver fat increase between baseline and follow-up. -Large interindividual variations in DNL and SCD16.
37. Low hepatic stearoyl-CoA desaturase 1 activity is associated with fatty liver and insulin resistance in obese humans.	Stefan, 2008 *Diabetologia*, Germany	n = 54 26(M)/28(F) Age 44 ± 2 (23–65) Nine-month long intervention period with counselling for a healthier diet and physical activity. SCD18 only	BMI Baseline: 29.3 ± 0.6 (19.4–40.2) Follow-up after nine months: 28.4 ± 0.6 (18.6–38.1) Subjects were analysed according to body fat percentage: Lean (body fat percentage 26.5 ± 1)	-SCD18 was negatively associated with liver fat, but the association depended upon the participants BF%. -SCD18 was significantly negatively associated with change in liver fat between baseline and follow-up in the obese group, i.e., the higher the SCD18 estimates at baseline, the more liver fat could be predicted lost at follow-up. -Participants qualifying for the diagnosis of fatty liver disease, had significantly lower SCD18 than the other participants.

		Serum VLDL TGR Liver fat determined by spectroscopy. Prospective longitudinal study.	Obese (body fat percentage 35.6 ± 1) Baseline body fat average 31.0 (range 16.0–50.0). Follow-up body fat average 30.1 (range 7.3–54.9).	-It was concluded that sufficient SCD18 activity may become increasingly important in the regulation of liver fat as adiposity increases.

Table V

Associations by lipid fraction.

Studie	Subject data	SCD16 Association with anthropometric indicator(s)	SCD18 Association with anthropometric indicator(s)	Lipid fraction	Subject health
1. Fatty Acid Profile and Desaturase Activities in 7–10-Year-Old Children Attending Primary School in Verona South District: Association between Palmitoleic Acid, SCD-16, Indices of Adiposity, and Blood Pressure, Bonafini et al., 2020	n=243 children Age: Male 8.7/Female 8.6 <u>BMI</u> Excess weight (n=88) 21.7 (± 2.8) Normal weight (n=155) 16.3 (± 1.7) <u>WHR</u> Excess weight 0.51 (± 0.77) Normal weight 0.43 (± 0.07) <u>Fat mass</u>	BMI Significant positive association WtHR Significant positive association (before adjustment for BMI) Fat mass Significant positive association (before adjustment for BMI)	BMI Negative association, but not significant. WtHR Negative association, but not significant Fat mass Negative association, but not significant	Whole-blood	Primary school children in the Verona South district Healthy prepuberal primary school children (age range (7–10)) were recruited from four primary schools in the Verona south district. They completed questionnaires regarding habitual food intake and physical activity.

	Excess weight 12.9 (± 5.36) Normal weight 5 (± 2.29)				
2. Desaturase Activity Is Associated With Weight Status and Metabolic Risk Markers in Young Children, Wolters et al., 2015	Baseline: Age: 2.1–9.7 years. Classified according to BMI (%): Thin: 6.4 Normal: 50.0 Overweight: 23.4 Obese: 20.2 Follow-up: Age: 3.9–11.7 Thin: 6.8 Normal: 50.5 Overweight: 22.8 Obese: 19.9	BMI -Significant positive association both at baseline and after two years. -Because the association was attenuated at follow-up, SCD16 indices at baseline did not have a significant predictive effect on BMI two years later.	Not estimated	Whole blood fatty acids The participants were.	Fasted Healthy children recruited from kindergartens and primary schools; From a larger representative sample a group of overweight and obese children were intentionally overrepresented.
3. Fatty acid profile and estimated desaturase activities in whole blood are associated with metabolic health,	n=321 <u>Normal weight</u> MH - (n=64) MU (n=11) <u>Age</u> MH 57.3 ± 14.9 MU 64.0 ± 11.4	BMI No association independent of metabolic health	BMI No association independent of metabolic health	Whole blood	MH and MU subjects classified as MH if had normalised TG levels, total cholesterol, LDL and HDL as well as glucose regulation. -Had one year earlier participated in a eight-week long controlled trial with lifestyle changes

Svendsen et al., 2020	<u>BMI</u> MH 22.7 (+/- 1.5) MU 23.9 (+/-0.8) <u>Overweight</u> MH - (n=52) MU (n=23) <u>Age</u> MH 55.6 ± 14.6 MU 63.9 ± 11.2 <u>BMI</u> MH 27.1 ± 1.3 MU 27.2 (±1.4) <u>Obese</u> MH (n=34) MU (n=18) <u>Age</u> MH 51.7 ± 14.4 MU 53.9 ± 11.2 <u>BMI</u> MH 33.3 (± 3.4) MU 33.8 (± 3.6)				
4. Effect of weight loss on circulating fatty acid profiles in overweight subjects with high visceral fat area: a 12-week	n=75 **Weight-maintenance group** n = 38 Age 46.0 ± 1.35	SCD16 BMI (and weight) Potential positive association	SCD18 BMI Not associated VAT Not associated	Total serum FAs	Non-diabetic, otherwise healthy subjects with a BMI between 25 and 30 kg/m2 and high L4 VAT (≥100 cm2). Subjects were divided into two groups: a weight-loss group with 12 weeks of mild calorie restriction (a 300 kcal/day intake

randomized controlled trial, Lee et al., 2018	Male/female 11 (28.9)/27 (71.1) <u>BMI:</u> Baseline: 27.3 +/- 0.25 Follow-up: 27.4 +/- 0.24 (change 0.17 (0.04) **Weight-loss group** n = 37 Age 44.1 ± 1.92 <u>BMI:</u> Baseline: 27.3 +/- 0.23 Follow-up: 26.4 +/- 0.24 (change -0.90 (+/-0.08).	VAT Positive, but non-significant association.			reduction) or a control group with no treatment.
5. Associations Among Fatty Acids, Desaturase and Elongase, and Insulin Resistance in Children, Beccarelli et al., 2018	Age: 9-12. BMI for age percentile: Normal weight 17.3 (+/-1.3) Overweight 21.0 (+/-0.9) Obese 26.2 (+/-3.1)	<u>BMI</u> No association <u>WC</u> No association	<u>BMI</u> No association <u>WC</u> No association	Plasma total lipids Fasted	Randomly selected school children participating in a study on obesity prevention. The participating children at the end of the study had a comparatively lower average BMI than controls (Scherr, 2018), meaning than the participants may have health wise not be representative.

6. Plasma palmitoleic acid content and obesity in children, Okada et al., 2005	Age: approx. 10-13 <u>Obese</u> BMI: 29.5 (±4.92) RW: 158.3 % (± 23.5) WC: 89.2 ± 12.1 <u>Non-obese</u> BMI: 17.9 ± 1.7 RW: 95.7 % ± 9.1 WC: Not detectable	<u>BMI</u> Significant positive association <u>WHR</u> Significant positive association <u>Percentage body fat</u> Positive association, but not significant.		Plasma total lipids	Fasted The subjects were a group of obese children free from any known illnesses in addition to a control group of non-obese healthy children. -The children were not dieting or participating in physical training. -Recruited from an outpatient clinic of the Nihon University School of Medicine, University of Tokyo. -Obesity was defined as having a RW >120% of predicted for sex, age, and height according to defined Japanese standards. -Control subjects were healthy schoolchildren with a RW <120% of the mentioned predicted standards. They were recruited through a screening and care program for lifestyle-related diseases in schoolchildren. -Study's variables included anthropometric measurements, serum lipids, leptin, and FA composition in plasma.
7. Plasma stearoyl-CoA desaturase indices: Association with lifestyle, diet, and body composition, Vinknes et al., 2013	n=2021 (924M/1097W) Age: 71-74 <u>Men</u> BMI 26 Overweight 62,6 % Obese 8,7 % <u>Women</u> BMI 26,1	BMI Significant positive association Body fat Significant positive association	BMI Significant positive association Body fat Significant positive association	Plasma total lipids	Non-fasted Randomly selected participants from age specific cohort

	Overweight 58,8 % Obese 16.7 %				
8. Association between increased visceral fat area and alterations in plasma fatty acid profile in overweight subjects: a cross-sectional study, Kang et al., 2017	Age: 40.2 (±0.68) Classified according to size of visceral fat area (VAT): T1: <71.8 cm2 T2: ≤ 71.8 cm2 - 99.6 cm2 T3: > 99.6 cm2 BMI T1: 26.8 (±0.17) T2: 26.7 (±0.16) T3: 27.3 (±0.16)	BMI No association VAT Significant positive association	BMI No association VAT Significant positive association	Plasma total lipids	Fasted Healthy overweight participants were recruited through advertisements (ie with a BMI between 25.0 kg/m2 and 30 kg/m2). Subjects with a history of intentional weight loss in the last 6 months were excluded.
9. Plasma palmitoleic acid, a product of stearoyl-coA desaturase activity, is an independent marker of triglyceridemia and abdominal	Age: 41 Analysis according to plasma TG percentiles: Below 75th n = 101 Age: 41	BMI Potential significant positive association, but possibly secondly to circulating TG levels	BMI Not evaluated WC Not evaluated	Plasma total lipids Fasted	Healthy unmedicated men with no previously known metabolic disorders. They did not follow any specific dietary recommendations.

adiposity, Paillard et al., 2008	At or above 75th percentile n = 33 Men only	WC Potential significant positive association, but possibly secondly to circulating TG levels			
10. Visceral fat thickness in overweight men correlates with alterations in serum fatty acid composition, Kishino et al., 2008	n=45 Men only Normal weight (n=21) Age 62 (±13) BMI 22 (+/- 1,9) Overweight (n=25) Age 56 (±13) BMI 27 (+/-2.7)	BMI Significant positive association VFT Significant positive association, but not independent of BMI.	BMI Not associated. VFT Not associated.	Serum total lipids	Fasted Normal-weight and overweight male hospital outpatients suffering from metabolic and "lifestyle-related diseases" (however not all participants had such symptoms).
11. Association of Plasma Lipids Fatty Acid Composition with Metabolic Profile of Czech	Age: 16.4 +/-0.9 BMI: Normal weight (defined as BMI between the 25th and	<u>BMI</u> No association <u>Fat mass</u> Significant positive association	<u>BMI</u> No association. <u>Fat mass</u> No association.	Plasma total lipids. Fasted	Participants selected from the Childhood Obesity Prevalence And Treatment (COPAT) Project. Selected from a general population including all body weight categories/

Adolescents, Hlavaty et al., 2015	75th percentile according to the age and gender) Overweight (BMI between the 25th and 75th percentile) Obese (BMI above the 95th percentile).				Normal, healthy adolescents aged 15.0-17.9 years from a general population including all body weight categories.
12. Palmitoleic acid is elevated in fatty liver disease and reflects hepatic lipogenesis, Lee et al., 2015	n=24 HighLF group n = 13 M 6/F 7 LowLF group n = 11 M 4/F 7 BMI LowLF group 35.3 ± 7.7 HighLF group 34.9 ± 5.2	SCD16 <u>BMI</u> <u>VLDL-TGR</u> Potentially no association <u>Liver fat</u> <u>VLDL-TGR</u> Significant positive association <u>FFA</u> Not significantly associated <u>DNL Measured</u> <u>VLDL-TGR</u>	SCD18 <u>BMI</u> VLDL-TGR Potentially no association <u>Liver fat</u> VLDL-TGR No association FFA Not significantly associated <u>DNL Measured</u> VLDL-TGR Not significantly associated	Fasting plasma VLDL-TGRs They also investigated associations in FFAs DNL (16:0/18:2n-6) estimates included	Non-diabetic, insulin resistant subjects with a BMI above 25 who were likely to have elevated DNL.

		Significant positive association <u>FFA</u> Significant positive association	FFA Significantly associated		
13. High Hepatic SCD1 Activity Is Associated with Low Liver Fat Content in Healthy Subjects under a Lipogenic Diet, Silbernagel	n = 20 (12M/8F) Age 30.5 ± 2.0 BMI: 25.9 ± 0.5 Intervention: Monosaccharides (600 kcal) added to a balanced diet for 4 weeks	BMI Not investigated. Liver fat Significant negative association with liver fat increase DNL (16:0/18:2n-6) Significant positive association with liver fat	Not estimated	Plasma VLDL TGR	Healthy individuals
14. Low hepatic stearoyl-CoA desaturase 1 activity is	n=54 Age= 45 26(M)/28(F) <u>BMI</u>	Not estimated	<u>Total body fat</u> Not associated <u>VAT</u> Not associated	Serum VLDL-TGR	Healthy participants recruited to an ongoing trial to reduce adiposity and prevent type 2 diabetes. -Included diet modifications and increased physical activity.

associated with fatty liver and insulin resistance in obese humans, Stefan	Baseline: 29.3 ± 0.6 (19.4–40.2) Follow-up: 28.4 ± 0.6 (18.6–38.1)		<u>Liver fat</u> Significantly negatively associated, but association depended on FM%.		-Recruitment criteria: Individuals with BMI above 27 and/or previous diagnosis of impaired glucose tolerance or gestational diabetes.
15. Fatty acid metabolism is altered in non-alcoholic steatohepatitis independent of obesity. Metabolism, Walle	n = 92 Age: 46.8 ± 9.5 years 30M/62F BMI Normal liver: 43.7 ± 6.9 Steatosis 44.5 ± 4.6 Steatohepatitis 44.7 ± 6.3	SCD16 <u>BMI</u> Was not investigated, but association cannot be excluded. Control study: Potential significant association <u>Liver fat</u> Significant positive association, potentially independently of BMI. Control study:	Not estimated	Significant associations in serum CE only, and not in TGR and PL.	Cross-sectional. Participants received obesity surgery at Kuopio University Hospital. Participants with diabetes were not excluded. Control study: Cross-sectional, population based randomly selected sample of men

		Significant positive association, but significance was lost when adjusted for among other BMI. <u>WC:</u> Control study: Potential positive association.			
16. Plasma lipid fatty acid composition, desaturase activities and insulin sensitivity in Amerindian women, Vessby et al., 2012	<u>Shuar women</u> n=59 Age: 35,7 years (+/-12) BMI: 23.6 (+/-2.7) <u>Lima women</u> n = 141 Age: 40 years (+/-11,1) BMI: 25.9 (+/-4.9) <u>Swedish women</u> n= 295 Age: 40,6 (+/-9,9)	BMI Significant positive association in the three groups Fat mass Significant positive association, but not significant among the Shuar-women	Not estimated	Plasma CEs Only data for cholesteryl esters were given, but they stated that the results were similar in all lipid fractions (i.e. cholesteryl esters, triglycerides and phospholipids)	Three groups of women: 1. From the Shuar settlements, an Andean community in the Amazonian rainforest - Had maintained a traditional hunter/gatherer lifestyle. 2. Women from Lima. All had ancestors from indigenous Andean communities 3. Healthy women from Uppsala, Sweden.

	BMI: 23.7 (+/- 3.8)				
17. Serum phospholipid and cholesteryl ester fatty acids and estimated desaturase activities are related to overweight and cardiovascular risk factors in adolescents, Steffen et al., 2008	Age: 15±1.2 years. Normal weight 20.5 Overweight 28.2	BMI CE Significant positive association PL Not associated Associations did not withstand further testing.	Not estimated	Serum cholesterol esters and phospholipids	Fasted Randomly selected adolescents from a school population, recruited according to strata of gender, ethnicity and blood pressure percentiles (one-half in the upper 25 percentiles and one-half in the lower 75 percentiles).
18. Effects of two-months balanced diet in metabolically healthy obesity: lipid correlations with gender and BMI-related differences, Rondanelli et al., 2015	Age:42.2 ± 9.5) Overweight (BMI < 30): 55 Obese (BMI > 30): 48	BMI: No significant association.	BMI: Significant negative association at baseline, but not at follow-up.	Serum phospholipids and cholesterol esters	Fasted -To be classified as MHO they had values within the normal range in the following categories 1. Triglyceride metabolism, 2. Cholesterol regulation 3.+4. Lipoprotein metabolism (HDL and/or LDL) and 5. Insulin sensitivity -Subjects were provided with compliance strategies and dietary plans according to the American Diabetes Association. -It was aimed at individual diet plans for weight loss of 0.5 to 1 kg per week.
19. Fatty acid composition in	n = 287 48F/52M Age 70	SCD16 BMI	Not estimated	Serum CE and PL	Randomly selected men and women from the population-based PIVUS cohort study; they

serum cholesterol esters and phospholipids is linked to visceral and subcutaneous adipose tissue content in elderly individuals: a cross-sectional study, Rosqvist (2017)	BMI 26.8 ± 4.	In CE and PL: Potential significant positive association SAT In CE and PL: Significantly positively associated Body fat percentage In CE and PL: Significantly positively associated Trunk fat In CE, but not PL: Significantly positively associated VAT In CE and PL: Not associated			were 70 years of age between 2001 and 2004 and lived in Uppsala, Sweden.

20. Fatty acid composition and estimated desaturase activities are associated with obesity and lifestyle variables in men and women, Warensjø et al., (2006)	n=849 Men 554 Women 295 Age Men - 40.6 (9.1) Women - 40.6 (9.9) BMI Men 24.7 (±3.2) Women 23.7 (±3.8)	BMI Significant positive association WC Significant positive association SAD (VAT): Significant positive association	BMI No association WC No association SAD (VAT): No association	Serum cholesterol esters	-Healthy employees in a telephone company. -Completed questionnaires regarding various lifestyle variables.
21. Serum Fatty Acids, Desaturase Activities and Abdominal Obesity – A Population-Based Study of 60-Year Old Men and Women, Alsharari et al., 2017	Age: 6o Men 1883 Females: 2015	BMI Not investigated in statistical analysis WC Significant positive association. WHR Significant positive association. VAT (SAD)	Not estimated	Serum cholesterol esters	Fasted Healthy men and women randomly selected from a population-based cohort of 60-year-old men and women living in the Stockholm, Sweden. Data collected end 1990s.

		Significant positive association.			
22. Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men, Warensjø et al., (2005).	n=1360 (baseline) n=706 (follow up) Men only Age 50 at baseline and 70 at follow-up. Baseline: Developed the metabolic syndrome: BMI: 23.9 (±2.4) Developed the metabolic syndrome: BMI: 25.6 (±2.5)	<u>SCD16</u> <u>BMI</u> Significant positive association. <u>WC</u> Significant positive association, but not independently of BMI. <u>SAD</u> Significant positive association, but not independently of BMI.	<u>SCD18</u> No significant associations.	Serum cholesterol esters	Fasted -Metabolically healthy subjects recruited from the Uppsala Longitudinal Study of Adult Men This study started in Uppsala, Sweden -Participants were examined at baseline at age 50 years (1970s) and at follow-up at the age 70 (1990s). -To classify as having developed the metabolic syndrome during the study period, abnormalities in three or more of the following risk determinants had to be present: 1. Glucose, 2.Blood pressure, 3. Triglyceride level, 4.Cholesterol concentration, and/or 5.Elevated WC.
23. Serum fatty acid composition and insulin resistance are independently	BMI 26.3 ± 3.4 WC 95.1 ± 9.2	SCD16 <u>BMI</u> Not investigated		Serum CEs and DNL (16:0/18:2n-6)	-A cohort of healthy 70 year old Swedish men randomly selected from the population based «Uppsala Longitudinal Study of Adult Men" study.

associated with liver fat markers in elderly men, Petersson		Liver fat (estimated by ALT): Significant positive association. WC Potentially not associated independently of liver fat.			-Participants with known previous liver disease or excessively high alcohol intake were excluded.
24. Associations between estimated fatty acid desaturase activities in serum lipids and adipose tissue in humans: links to obesity and insulin resistance, Warensjø et al., (2009)	n=301 Age: 63 (0.7) Men only BMI 25.9 (±3.1)	BMI Phospholipids: Significant positive association Free fatty acids: Significant positive association AT-TAG Significant positive association	BMI Phospholipids: Negative association Free fatty acids: Positive association Adipose tissue TAG: Significant positive association	Serum PLs and serum FFAs As well as adipose tissue TGRs	Fasted The subjects were healthy 60-year-old Swedish men randomly selected from a cohort study among Swedish men and women from Stockholm.
25. Association of Changes in Body	Age: 9.6 (±0.5)	RW: No association	RW Significant negative association among	Plasma PLs	Fasted

Fatness and Fatty Acid Composition of Plasma Phospholipids during early Puberty in Japanese Children, Abe (2012)	RW adjusted for age/gender and height (baseline/follow-up): Boys Non-obese 102,8 (±12,4)/ 93.7±8.5 Obese: 145,4 (±31,8)/ 131.7±22.6 Girls: Non-obese 101 (1±11,9)/ 98.0±12,1 Obese: 139,4,4 (±13,7)/ 134.1(±15.3)	WHtR: No association	boys phase one and two, and significant change. WHtR: Significant negative association among boys phase one and two, and significant change.		Healthy Japanese elementary school children free from diseases, except possible dyslipidaemia and/or obesity
26. Associations Between Estimated Desaturase Activity and Insulin Resistance in Korean Boys, Choi (2014)	Boys only. Age 10.5 ± 0.4 BMI adjusted according to age and gender (baseline/follow-up):	BMI Baseline: Significant positive association Follow-up: No significant association, but significance	BMI No significant association (negative direction) WC No significant association (negative direction)	Plasma phospholipids	Fasted Participants recruited from the Korean Children and Adolescent Cohort Study which follows a student cohort from the time of entry into elementary school to graduation in Seoul and the Kyunggi provinces in Korea.

	Lean (18.2 ± 0.5/18.8 ± 0.8) Intermediate (21.7 ± 1.0) Obese (23.8 ± 2.3/26.2 ± 3)	remained if just comparing lean and obese children. WC Baseline: Significant positive association Follow-up: No significant association			
27. Changes in SCD gene DNA methylation after bariatric surgery in morbidly obese patients are associated with free fatty acids, Morcillo, 2017	Age: 43.2 (± 9.4) Before surgery: Obese, grade 3 After surgery: Obese, grade 2 Control: Age: 47.2 ± 5.8 Obese, grade 1	BMI Potential positive association WC SCD16 Potential positive association	BMI Potential positive association WC SCD18 Potential positive association	Serum phospholipids	Fasted Patients scheduled for bariatric surgery.
28. Docosahexaenoic Acid Content in Plasma Phospholipids and Desaturase Indices	Age: 12.0 (±2.6) years BMI 29.1 +/-5.0 (M) 29.0 +/-5.9 (F)	BMI Significant positive association WHtR	BMI Significant positive association WHtR Not associated	Plasma phospholipids	All children had abdominal obesity (measured by WHtR), and five had the metabolic syndrome.

in Obese Children, Saito (2011)		Significant positive association			
29. Relationship between estimated fatty acid desaturase activities and abdominal adiposity in Japanese children, Saito 2014)	Without/with abdominal obesity men: 0.42 ± 0.03 (M) /0.58 ± 0.05 (M) Without/with abdominal obesity females: 0.43 ± 0.03 (F))/0.57 ± 0.05 (F)	Not estimated	POW Potential association WHtR Potential U-shaped association since both children with and without high WHtR had high SCD18 activity estimates.	Plasma phospholipids (fasted)	Fasted Children were free from diseases other than dyslipidemia and obesity or abdominal obesity. Recruited from a school-based screening and care program for life-style related diseases at an out-patient clinic.
30. Association between serum phospholipid fatty acid levels and adiposity in Mexican women	BMI 30.3 +/- 5.2 WHR 0.91 ± 0.06	BMI Significant positive association WC Significant positive association WHR Positively associated, but	BMI Significant negative association, significance lost in ANCOVA analysis WC Significant negative association, significance lost in ANCOVA analysis WHR	Serum phospholipids	Healthy controls (non-cancer cases) from a population-based case-control study on breast cancer.

		not significantly	Not associated		
31. Comparison of dietary and plasma phospholipid fatty acids between normal weight and overweight black South Africans according to metabolic health: The PURE study, Ojwang, 2020.	n = 711 345 MHNW 79 MUNW 120 MHO 167 MUO Age: 51 MHNW 51 MUNW 49 MHO 55 MUO <u>BMI</u> 19.8 (17.8-22.0) MHNW 21.4 (19.1-23.3) MUNW 30.4 (26.9-34.1) MHO 31 (27.6-34.5) MUO	BMI Within BMI-groups Potential positive association Between BMI groups Significant negative association Metabolic health Within BMI groups Negatively associated	BMI Within BMI-groups Potential positive association Between BMI groups Significant negative association Metabolic health Within BMI groups Negatively associated	Plasma PL	Fasted -Participants categorised as metabolically healthy normal weight (MHNW), metabolically unhealthy normal weight (MUNW), metabolically healthy overweight/obese (MHO) and metabolically unhealthy overweight/obese (MUO). -MetS defined as having abnormalities in three or more of the following criteria: 1. Glucose regulation, 2. Triglycerides,3. Lipoprotein composition, 4. Blood pressure or 5. Large WC
32. Serum Phospholipid Fatty Acids Levels, Anthropometric Variables and Adiposity in Spanish Premenopausal Women,	Females only n=1443 Age: 44.3 (2.8) BMI 24.3 (+/- 4.3) WC 80.0 (+/-11.2) Body fat percentage	BMI Significant positive association Visceral fat and weight gain since age 18:	BMI Significant negative association WC Weak positive association after adjustment for BMI	Serum phospholipid fatty acids.	Randomly selected study population, with normal, average health.

Del Pilar del Pozo et al., (2020).	30.3 (+/-7.3) Waist-to-hip ratio 0.8 (+/-0.1) Visceral fat index 5.2 (+/-2.4)	No significant association independent of BMI			
33. Association between Serum Phospholipid Fatty Acid Levels and Adiposity among Lebanese Adults: A Cross	n=395 129M/266W Age: 44.5 ± 15.3 BMI Men: Underweight and normal (<25): 32.6% Overweight (25–29.99): 37.2% Obese (≥30): 30.2% Women: Underweight and normal (<25): 22.9% Overweight (25–29.99): 31.6% Obese (≥30 kg): 45.5% WC Men	<u>BMI</u> Significant positive association among women (significance lost when tested for false discovery rate). <u>WC</u> Significant positive association among women (significance lost when tested for false discovery rate).	<u>BMI</u> Significant negative association among women. <u>WC</u> Significant negative association among women.	Serum phospholipids	Representative sample of Lebanese adults living in the greater Beirut area with no prior history of chronic diseases.

	96.1 (± 12.7) Kvinner 93.8 (± 16.4)				
34. Relationship between the estimates of desaturase activities and cardiometabolic phenotypes in Koreans	n=93 36 men and 57 females Age= 54.4 ± 13.4 BMI = 23.3 ± 2.7	BMI Significant positive association WC Not significantly associated (positive direction)	BMI Not significantly associated (negative direction) WC Not significantly associated (negative direction)	Serum phospholipids	Healthy volunteers. Fasted No information regarding recruitment process.
35. Fatty Acid Composition of Plasma Phosphatidylcholine Determines Body Fat Parameters in Subjects with Metabolic Syndrome-Related Traits	Study group Age 47 (40-55) BMI 27.9 (25.4-30.9) Healthy controls Age 43 (33.2-54.8) BMI 23.2 (21.3-25.1)	BMI Potential significant positive association WC, WHR and body fat percentage. Potential positive association	BMI Not significantly associated, but negative direction. WC, WHR and body fat percentage. Potential negative association	Plasma PL phosphatidyl choline	-An overweight study group with metabolic syndrome-related traits and a normal weight healthy control group. -The study group had central obesity (83%) as defined by the International Diabetes Federation in addition at least one other component of the metabolic syndrome (abnormal glucose regulation, high TGRs, 3. Abnormal lipoprotein composition or 5. Hypertension

36. Associated factors of estimated desaturase activity in the EPIC-Potsdam study	n = 1782 Total age: 35–65 Age quintiles based on SCD16 estimates: Q1 49.68 (±8.99)/ Q5 52.31 (±8.55 <u>BMI</u> quintiles according to SCD16 activity estimates: Q1: 25,21 (±3.80)/Q5: 27.09 (±4.34)	BMI Positive association. WHR Positive association.	Not estimated	Erythrocyte membrane phospholipids	Recruited from the general population
37. Fatty Acid Profile of Mature Red Blood Cell Membranes and Dietary Intake as a New Approach to Characterize Children with Overweight and Obesity, Jauregibeitia (2020)	n = 209 Age: 6 – 16 113M/96W Classified as normal weight (n = 107), overweight (n = 41) or obese (n = 61) according to BMI.	BMI Not significantly associated	BMI Significant negative association	Red blood cell phospholipid membranes	Fasted Generally healthy children chronic diseases and metabolic or obesity related pathology.

Table VI

Studies that had included dietary data

Study	Had included dietary data	Had not included dietary data
1.Beccarelli, 2018.	X	
2.Hlavary, 2015.		x
3.Okada, 2015.		x
4. Morcillo, 2017.	X (pre-surgery VLCD)	
5.Choi, 2014.		X
6.Abe, 2012.		X
7.Kang, 2017.		X
8.Wolters, 2015.	X (intervention)	
9.Steffen, 2008.	X	
10. Rondanelli, 2015.	X (intervention)	
11. Saito, 2011.		X
12. Saito, 2014.		X
13. Zeman, 2017.		x
14.Aglago2017.	X	
15.Ojwang, 2020.	X	
16.Vessby, 2012.	X	
17.Del Pilar del Pozo, 2020.	X	
18.Lee, 2018.	X (intervention)	
19.Paillard, 2008.		X
20. Svendsen, 2020.	X (intervention)	
21. Schiller, 2014.	X	
22.Warensjø, 2005.	X	
23.Warensjø, 2006.	X	
24. Warensjø, 2009.		X

25.Vinknes, 2012.	X	
26.Bonafini, 2020.	X	
27.Yammine, 2018.	X	
28.Jauregibeita, 2020.	X	
29. Kishino, 2008.		X
30. Do, Chung, Moon & Shin, 2011.		X
31. Alsharari, 2017.		X
32.Walle, 2016.	X (pre-surgery VLCD)	X (Control study)
33.Lee, 2015.	X (intervention)	
34.Petersson, 2010.	X	X
35.Rosqvist, 2017.	X	
36.Silbernagel, 2012.	X (intervention)	
37.Stefan, 2008.	X (intervention)	