Abating abdominal adiposity: Modifiable lifestyle risk factors for visceral and liver fat deposition

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General introduction, study population and outline of this thesis

The objective of this thesis was to study the role of dietary habits and physical activity in abdominal fat accumulation, which is a well-established risk factor for cardiometabolic diseases. This general introduction describes the epidemiology and historical perspective of overweight and obesity, the current knowledge about how diet and physical activity may influence visceral fat and liver fat, and how the research described in this thesis may contribute to addressing the gaps in knowledge that still exist.

Overweight and obesity: prevalence and relation to disease

Obesity is characterized as a condition in which excess energy is stored in the form of triglycerides in adipose tissue, which may ultimately cause health impariment [1]. In order to classify obesity the World Health Organization uses the body mass index (BMI). It is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). Based on this index, the World Health Organization has made the following classification: underweight (<18.5 kg/m^2), normal weight (18.5-24.99 kg/m^2) and overweight (>25.0 kg/m^2). Because management options regarding prevention and treatment of obesity differ above a BMI of 35, the overweight category can be further subdivided into the following categories: preobese (25.0-29.99 kg/m^2), obese class I (30.0-34.99 kg/m^2), obese class II (35.0-39.99 kg/m^2) and obese class III (≥40.0 kg/m^2). In a large systematic analysis of health examination surveys and epidemiological studies it has been shown that between 1980 and 2008 the age-standardized mean global BMI has increased by 0.5 kg/m^2 in both men and women per decade [2].

In 1980, the global prevalence of overweight was 25% and that of obesity 6%. These numbers have increased to 34% for overweight and 12% for obesity in 2008 [3]. In absolute numbers this represents an increase from 572 million adults with overweight worldwide in 1980 to almost 1.5 billion in 2008, of whom 508 million with obesity [3]. This number has continued to rise even further to 670 million adult obese individuals in 2016, of whom 390 million were women and 280 million men. By 2020 2.2 billion adults will have overweight and 1.1 billion of them obesity when recent secular trends are taken into account [4]. This trend is also visible in the Netherlands: in 2018 half of all adults (50.2%) had overweight and 15% of them had obesity [5].

Excess body fat is an established strong risk factor for multiple chronic diseases, such as type 2 diabetes, cardiovascular disease and certain types of cancer. In 2015, overweight and obesity accounted for 4 million deaths, which contributed to a little over 7% of the deaths from any cause that year. Overweight was also responsible for 120 million disability-adjusted life-years [6].

Obesity and weight gain have been associated with an increased risk of diabetes [7,8], and those with a BMI of 40 or higher are 7 times more likely to be diagnosed with diabetes than those with a normal BMI [9]. The relation is so strong, that it is thought that 90% of type 2 diabetes is attributable to excess weight [10]. Both overweight and obesity are also related to the risk of developing cardiovascular risk factors such as hypertension, and as a consequence a BMI of 25 accounts for 35% of hypertension diagnoses in men and 60% in women [11]. An increased risk due to overweight was also found for coronary heart disease and cerebrovascular disease in both men and women in large cohort studies such as the Nurses' Health Study, the Dallas Heart Study and the Physicians' Healthy Study [12]. At a global level, 41% of high BMI-related deaths were caused by cardiovascular disease among people with obesity, and diabetes was the second largest cause [6]. In both men and women, a high BMI has also been associated with an increased risk of death due cancer of the esophagus, colon and rectum, liver, gallbladder, pancreas and kidney, and with non-Hogdkin's lymphoma and multiple myeloma [13]. A dose-response relationship, in which the risk of death increases with higher BMI, was found for stomach and prostate cancer in men and breast, uterus, cervix and ovary cancer in women [13].

Multiple studies have found that a high BMI is a strong risk factor for end stage renal disease [14]. Obesity has also been linked to knee osteoarthritis due to the increased load on these weight-bearing joints, and other joint-related disorders such as gout [12]. Additionally, excess body weight increases the risk of pancreatitis, ischemic dementia, Alzheimer's disease and psychological problems, such as mood and anxiety disorders [12].

Body fat distribution and ectopic fat

Although BMI is a widely-used and easy to measure proxy for overall adiposity, it does not take body composition into account. A high BMI does not necessarily indicate a high body fat percentage, as it might also be the consequence of larger muscle mass. Moreover, BMI does not consider where exactly the fat is stored in the body.

Already in 1947, Vague discovered that patients with hypertension, diabetes or cardiovascular disease were not per definition more obese than those without complications [15]. He did, however, observe that individuals who had more fat stored in the trunk area had an increased risk of diabetes and cardiovascular disease. As a result, he identified two body shapes and formulated the terms *gynoid obesity* and *android obesity* [15]. Nowadays, we still use these terms: android obesity is characterized by a large waist circumference with the majority of the adipose tissue centering around the abdomen, more commonly found in men. In contrast, in a gynoid or pear shaped body type most adipose tissue is stored subcutaneously at the hips, buttocks and thighs, often going

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hand in hand with a smaller waist circumference. This body type is more common in women.

In the early 1980s, another breakthrough in the field of obesity was accomplished. Björntorp and his group discovered that body shape, and thereby the regional accumulation of body fat, and the morphology of this fat were closely related to metabolic diseases [16]. Subsequently, they described that men with a high proportion of abdominal fat had a substantially increased risk of developing diabetes [17]. These discoveries have sparked the interest of the medical community and laid the foundation for the research on body fat distribution we do today.

After the development of imaging techniques such as computed tomography (CT), it became possible to scan the whole body and discriminate between different types of tissue. Researchers from the University of Osaka were the first to use the CT for this purpose, and were able to distinguish the fat located in the abdominal cavity, or visceral fat, from the fat located subcutaneously [18]. A few years later, in 1987, they were the first to show the detrimental effects of viscerally stored adipose tissue, by demonstrating that subjects with more visceral adipose tissue displayed higher fasting plasma triglycerides levels and higher plasma glucose responses following an oral glucose challenge than those with the same BMI but fat mainly stored subcutaneously [19]. In 1989, Seidell showed that visceral fat area as measured with CT was also associated with serum triglycerides, plasma insulin, glucose and diastolic and systolic blood pressure [20].

These landmark studies in combination with more recent developments have shown that the majority of lipids accumulate in subcutaneous adipose tissue, which is located just below the skin and amounts to 82-97% of total body fat. Subcutaneous adipose tissue has the capability to expand when there is a positive energy balance. However, the response to excess caloric intake might vary, and there is considerable variation between individuals where the fat is stored [21]. Lipids can also accumulate in visceral adipose tissue, which is located deeper in the body and situated around the organs, and amounts to 10 to 15% of all fat [22]. Additionally, lipids can be stored in non-adipose tissue cells, such as in the liver (intrahepatic fat) or the muscles (intramuscular fat). This is referred to as ectopic fat.

There are large sex-related differences in the location of fat deposition. On average, women have a higher percentage of body fat than men for the same BMI and are more likely to store fat subcutaneously in the femoral gluteal region. Men, however, store more fat in the visceral area [23, 24]. These differences are caused by multiple factors, such as differences between men and women in basal fatty acid oxidation, postprandial fatty acid storage, and regional differences in the regulation of lipolysis [23]. As postmenopausal women are more likely to store fat viscerally than premenopausal women, testosterone levels also seem to be important in body fat distribution [25].

Furthermore, studies in identical twins have shown that the susceptibility to store fat either viscerally or subcutaneously is partly determined by genetics [26-28], and multiple loci associated with visceral adipose tissue have been identified in genome wide association studies, of which some appear sex-specific [29]. Additionally, age, ethnicity, physical activity and levels of glucocorticoids have also been associated with visceral fat accumulation [30]. Due to the large individual variation in adipose tissue depots and various factors contributing to these differences in deposition, obesity is a surprisingly heterogeneous condition iwhenit is defined based on BMI alone [30], as it has been shown that patients with similar BMI values present different levels of health risk [31].

In parallel to the increase in obesity over the past decades, the prevalence of non-alcoholic fatty liver disease (NAFL) also continues to rise and is now present in 25% of the general adult population, and 65% to 85% in adults with obesity [32]. Non-alcoholic fatty liver disease is defined as having more than 5.56% of liver fat not due to excessive alcohol consumption [33] and may lead to non-alcoholic steatohepatitis (NASH) and liver cirrhosis. It also increases the risk of end-stage liver disease and liver-related and all-cause mortality [34-37]. Currently, it is the leading cause of chronic liver diseases worldwide [38], and is also strongly related with the metabolic syndrome [39] and cardiovascular diseases [40]. In previous research, visceral adipose tissue and hepatic triglyceride content have both been associated with insulin resistance, metabolic risk factors and cardiovascular disease [41-44]. Since the first state of NAFL, simple steatosis, is still reversible, adequate treatment is needed [45, 46].

The overflow hypothesis explains fat accumulation in liver and visceral area, and states that the body's response to excess calories may determine the risk of the metabolic syndrome [47]. When the caloric surplus is led into the subcutaneous adipose tissue, which is sensitive to insulin, the individual is unlikely to develop the metabolic syndrome as the subcutaneous fat can expand. When, however, this adipose tissue is not functioning properly or if it is insulin resistant with an insufficient capacity to store the extra energy, the fatty acids will be stored in visceral adipose depots, in turn leading to ectopic fat disposition. Therefore, according to the lipid overflow hypothesis, accumulation of visceral fat is a marker of dysfunctional subcutaneous fat [30]. In the liver, the increased free fatty acid flux observed in individuals with obesity [47] leads to increased hepatic lipase activity. In turn, this causes reduced hepatic degradation of insulin and apolipoprotein B and increased hepatic glucose production, leading to glucose intolerance [48]. Moreover, visceral fat is also associated with an increased risk of respiratory diseases such as sleep apnoea or chronic obstructive pulmonary disease (COPD), dementia, reduced bone density, polycystic ovary syndrome and different types of cancer [49]. It decreases adiponectin secretion, and together with liver fat thereby brings about hypertension, insulin resistance, dyslipidaemia, and ultimately atherosclerosis [50]. Both visceral fat and liver fat have been associated also with coronary artery disease and cardiovascular disease [41, 43].

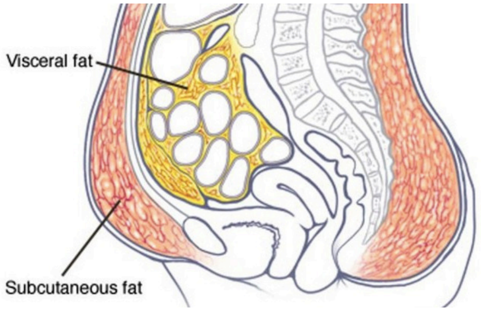

Figure 1. Subcutaneous fat and visceral fat in the abdomen

Diet as a modifiable risk factor for visceral fat and liver fat

Visceral fat and liver fat are key targets in the prevention and treatment of cardiometabolic diseases. Due to a lack of drug-based treatments, modifiable lifestyle factors such as dietary habits and physical activity are key when it comes to the prevention and treatment of abdominal obesity [45]. Dietary habits can be studied on multiple levels. To understand how particular components of food are related to disease, studying diet on a micro- or macronutrient level is useful. The main focus regarding decreasing body weight concerns caloric restriction. However, besides diet quantity, diet quality may also be important for health. An overfeeding trial of saturated and polyunsaturated fatty acids has shown distinct effects on visceral fat and liver fat [51], indicating the importance of dietary macronutrient composition for the accumulation of adipose tissue. Moreover, it has been proposed that specific nutrients, such as fructose, increase hepatic de novo lipogenesis [52]. Increased lipolysis of visceral fat can contribute to an increased flux of free fatty acids in the liver, which may ultimately lead to accumulation of triglycerides and other lipids in the liver [53]. Although some meta-analyses have been performed on specific micronutrients in relation to NAFL, results were inconclusive [54]. For subcutaneous and visceral fat, one systematic review on the effects of dietary aspects has already been published [55], and described an inverse relation between intake of medium chain triglycerides and dietary patterns recognized as healthy and subcutaneous fat and visceral fat. Dietary fiber and calcium were found to be negatively associated with visceral fat only. For liver fat, however, such an overview does not yet exist. Besides omega-3 polyunsaturated fatty acids and fructose consumption, little is known about the association between other macronutrient and macronutrient subtypes and liver fat.

As foods are not merely the sum of their nutrients, health effects of diet can be studied at the level of foods and food groups rather than single nutrients [56-58]. The food matrix may play a role, or interactions between the separate nutrients within a food item might occur [57-59]. In line with this, several European countries and the United States have published dietary guidelines that are based on food products and groups instead of single nutrients [60]. Previous studies have shown that major food groups such as meat, dairy and fruit and vegetables are associated with body weight [61], diabetes [62] and cardiometabolic diseases such as coronary heart disease (CHD) [63]. However, it remains unclear to what extent these food groups are specifically associated with visceral fat and liver fat. Knowledge on these potential associations might contribute to the development of new preventive guidelines regarding healthy dietary habits, or the adjustment of current guidelines in relation to cardio metabolic diseases.

Combining multiple food items or groups makes it possible to study dietary patterns as a whole. Dietary guidelines that have been developed on the basis of previous research state the optimal consumption of several food items and food groups. Adherence to these guidelines can be assessed using an index. Numerous dietary indices of adherence to a healthy diet have been developed recently, among which the (Alternative) Healthy Eating Index (HEI) [64], the Healthy Diet Indicator [65] and the Diet Quality Index (DQI) [66]. Research has shown that a higher index, indicating a better adherence to the dietary guidelines and therefore a healthier diet, is associated with a lower risk of obesity, cardiovascular disease and all-cause mortality [67]. In the Netherlands, the Health Council of the Netherlands has developed the Dutch Guidelines for a Healthy Diet, of which the newest version appeared in 2015 [68]. These new guidelines are mostly foods-based and describe the optimal consumption for food groups such as fruit and vegetables and dairy, but also consumption of unsalted nuts, green tea and filtered coffee. Adherence to these guidelines can be assessed using the Dutch Healthy Diet Index, which scores each component of the Dutch Guidelines for Healthy Diet. Using this index makes it possible to study to what extent adherence to the guidelines is associated with multiple health-related outcomes. Although the 2015 DHD-index is still recent, a higher score on the Dutch Healthy Diet Index 2015 has been associated with a decreased risk of stroke, chronic obstructive pulmonary disease, colorectal cancer and all-cause mortality [69]. However, it remains unclear to what extent adherence to the 2015 Dutch Guidelines for a Healthy Diet is specifically associated with the amount of visceral fat and liver fat.

Alcoholic and non-alcoholic beverages in relation to liver fat

Excessive alcohol consumption is a well-established risk factor for both hepatic steatosis (liver fattening) and liver disease [70]. Although current guidelines aim at preventing or reducing liver fat accumulation recommend to refrain from heavy alcohol consumption, it remains unclear whether moderate alcohol consumption should also be discouraged. Several studies have shown a beneficial effect of light to moderate alcohol consumption in relation to fatty liver and extra-hepatic complications [71-74]. However, a study using a genetic variant in the alcohol dehydrogenase gene as a proxy of long-term alcohol exposure showed no beneficial effect of moderate alcohol consumption on the severity of non-alcoholic fatty liver disease [75]. Even when alcohol use is discouraged, it it is unclear with what beverages patients with non-alcoholic fatty liver should replace their alcoholic drinks. We hypothesize that non-alcoholic energy containing beverages may also contribute to liver fat accumulation, as calories from these beverages contribute to the total energy intake and liquid food leads to less satiety and more postprandial hunger [76]. Knowledge on the association between different beverages and their mutual replacement with liver fat may contribute to lifestyle guidelines for both primary and secondary prevention.

Physical activity in relation to abdominal fat

Besides healthy dietary habits, physical activity is a key modifiable risk factor for obesity and cardiovascular disease. Energy balance within the body reflects a harmony between of energy intake, energy expenditure and energy storage. While diet provides the energy intake, energy expenditure consists of three components: the energy it takes to fuel the body at rest (resting metabolic rate, approximately 60-75% of total energy expenditure), the energy it costs to absorb and metabolize the food that is consumed (thermic effect of food, approximately 10% of total energy expenditure) and the energy expended by undertaking physical activity (approximately 15-30% of total energy expenditure) [77, 78]. When the energy intake is greater than the energy expenditure over a longer period of time, this will lead to excess storage of fat and thereby an increase in body weight [79]. Physical activity has been defined as 'any bodily movement produced by skeletal muscles that results in energy expenditure [80] and can be subdivided into multiple activity intensities. activity levels are usually expressed in Metabolic Equivalents of Task (METs), which assign an intensity value to each specific activity [81]. Light physical activity is defined as activities lower than 3.0 METs and includes activities such as sitting (1.5 MET), walking slowly (2.0 MET) or playing a musical instrument (2.5 MET). Moderate physical activity is defined as 3.0 to 6.0 MET, such as cleaning (3.0 MET), playing recreational badminton (4.5 MET) or mowing the lawn (5.5 MET). All activities above 6.0 MET are defined as vigorous [82].

Most European guidelines on physical activity recommend to perform at least 150 minutes of moderate to vigorous physical activity per week. Additionally, they state sedentary time should be limited [83], as this behaviour has been associated with increased risk of type 2 diabetes, cardiovascular disease and cancer [84]. A meta-analysis has shown that exercise is able to reduce both visceral fat and liver fat, although the studies that were included focused on structured exercise instead of habitual daily activities. Therefore, the evidence on the potential association between these so-called unstructured activities and sedentary time as assessed with accelerometry and different adipose depots is still lacking. Furthermore, less time spent sedentary inevitably means more time is spent performing other activities. In the study of a decrease of time spent in particular activity, it is therefore important to take into account with which activity this is being replaced (e.g., replacing sedentary time with the same time spent on moderate to vigorous physical activity). This can be done using isotemporal substitution analysis. However, most studies using this type of statistical model use surrogate outcomes for adiposity such as body mass index or waist circumference instead of directly assessed measures of adiposity [85]. Only one study has combined objectively measured physical activity and direct measures of visceral fat, and observed that isotemporal substitution of one hour per day of sedentary and light intensity physical activity with moderate to vigorous physical activity was associated with reduced visceral fat [86]. However, liver fat was not assessed in this study and no adjustment for total body fat was performed. Therefore, evidence on how replacing sedentary time with other activities is associated with directly assessed visceral fat and liver fat is still largely lacking.

OUTLINE OF THIS THESIS

Although many previous studies have investigated the health-related consequences of a healthy lifestyle, there is still much to be learned. Up to date, not much is known about how diet and physical activity affect visceral fat and liver fat. Therefore, the objective of this thesis was to study the role of dietary habits and physical activity in abdominal fat accumulation, more specifically in the visceral area and in the liver.

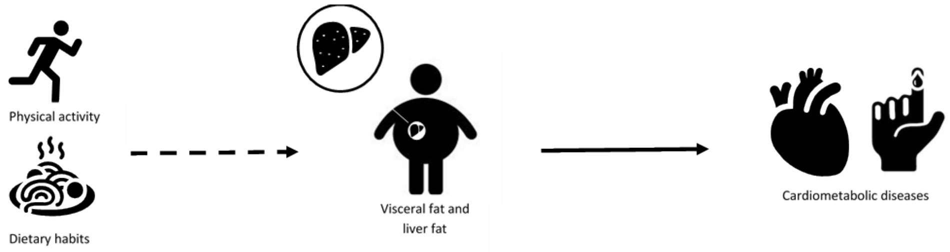

Figure 2. Visual representation of hypothesized association between dietary habits and physical activity and visceral fat and liver fat, ultimately leading to cardiometabolic diseases

In order to prevent non-alcoholic fatty liver from progressing to more severe forms of hepatic fat storage, such as non-alcoholic steatohepatitis or even liver cirrhosis, adequate treatment is needed.

The current treatment for non-alcoholic fatty liver disease is mainly focused on weight loss by means of calorie restricted diets [87-89]. However, besides diet quantity in the form of caloric restriction, the macronutrient composition of a diet may be important. In **Chapter 2** we performed a systematic review and meta-analysis on the effect of dietary macronutrient composition on liver fat in randomized controlled trials. Studies included in this meta-analysis compared diets high in one macronutrient and low in another with diets with the opposite composition and their effect on liver fat content.

As foods are not merely the sum of their nutrients, studying foods and food groups may be important in relation to multiple health outcomes [57] and is becoming more important in the development of dietary guidelines. In **Chapter 3** we examined the association between dietary intake of certain food groups, such as meat, fruit and vegetables and dairy, and visceral fat and liver fat specifically. We also investigated a finer categorization of these main food groups, to assess whether associations were driven by one component of that food group in particular.

Adherence to the Dutch Guidelines for a Healthy Diet, which are dietary guidelines that aim to decrease the risk of chronic diseases [90], can be measured using the Dutch Healthy Diet Index [91]. In **Chapter 4**, we aimed to examine whether the 2015 Dutch Healthy Diet Index is associated with both total body fat, visceral fat and liver fat. By leaving each component out one at a time, we tried to examine which component is most important in these associations.

Besides consumption of certain nutrients and food items or groups, excessive alcohol consumption is a well-known risk factor for liver fattening and liver disease [70]. Current guidelines to prevent or reduce liver fat accumulation recommend that heavy drinking should be refrained from [92]. However, it remains unclear what beverages should replace the alcohol when people are advised to refrain from further alcohol consumption. We hypothesized that energy-containing non-alcoholic beverages, such as sugar sweetened beverages, also contribute to the accumulation of liver fat, and investigated the association between both alcoholic and non-alcoholic beverages and liver fat in **Chapter 5**. We also assessed how replacing alcohol with non-alcoholic beverages is associated with liver fat.

Besides dietary habits, physical activity is another key modifiable risk factor for obesity and cardio metabolic diseases. In **Chapter 6** we investigated different levels of physical activity, such as sedentary behaviour, light, moderate and vigorous physical activity, in relation to total body fat, visceral fat and liver fat. In this study we have also used isotemporal substitution analysis to study the association between replacing 30 minutes of sedentary time with 30 minutes of another activity and the body fat measurements.
Lastly, **Chapter 7** summarizes important findings of this thesis and discusses their interpretation and clinical implications.

Population and design of the Netherlands Epidemiology of Obesity study
All studies described in this thesis, except for the meta-analysis, have been performed in the Netherlands Epidemiology of Obesity (NEO) study. This is a population-based prospective cohort study in 6 671 individuals aged 45 to 65 years, with an oversampling of persons with a BMI of 27 kg/m^2 or higher. All studies described in this thesis are based on the baseline measurements and therefore of a cross-sectional nature. Men and women aged between 45 and 65 years with a self-reported BMI of 27 kg/m^2 or higher living in the greater area of Leiden (in the West of The Netherlands) were eligible to participate in the NEO study. In addition, all inhabitants aged between 45 and 65 years from one municipality (Leiderdorp) were invited irrespective of their BMI, allowing for a reference distribution of BMI. To be able to make inferences on the general population, we weighted all analyses towards the BMI distribution of the Dutch general population using the distribution of the Leiderdorp participants. Consequently, all results described in this thesis apply to the general population.

Participants visited the NEO study center of the Leiden University Medical Center after an overnight fast. Prior to the NEO study visit, participants completed a questionnaire about demographic, lifestyle, and clinical information, in addition to a food frequency questionnaire. At the study center, the participants completed a screening form, asking

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about anything that might create a health risk or interfere with magnetic resonance imaging (MRI) (most notably metallic devices, claustrophobia, or a body circumference of more than 1.70 m). Of the participants who were eligible for MRI, approximately 35% were randomly selected to undergo direct assessment of abdominal fat. In total, 2,580 participants had a valid measurement of visceral adipose tissue by MRI, and 2,083 participants of hepatic triglyceride content by MRS. These imaging modalities allow direct assessment of visceral adipose tissue and hepatic triglyceride content, which is a unique feature of the NEO study as most epidemiological studies use composite measures to estimate abdominal adiposity. An overview of the main methods to assess overall body fat and abdominal fat can be found in **Table 1**.

The Medical Ethics Committee of the Leiden University Medical Center approved the design of the study. All participants gave their written informed consent.

Table 1. Commonly used measures of overall body fat and abdominal fat

Measure	Instrument	Validity	Feasibility in large epidemiological studies	Advantages	Disadvantages
Overall body fat					
Weight (kg)	Questionnaire or scale	Low	High	Easily measured in large epidemiological cohorts	Does not discriminate body fat and fat free mass
BMI (kg/m²)	Questionnaire or scale	Low	High	Easily measured in large epidemiological cohorts	Does not discriminate body fat and fat free mass
Total body fat (%)	Bio impedance balance	High	Low	Provides indication in the amount of adipose tissue in body	Does not discriminate between subcutaneous and visceral fat
Abdominal fat					
Waist circumference (cm)	Measuring tape	Intermediate	High	Easily measured in large epidemiological cohorts	No direct measure of abdominal fat
Waist-hip-ratio	Measuring tape	Intermediate	High	Easily measured in large epidemiological cohorts	No direct measure of abdominal fat
aSAT (cm²)	Magnetic resonance imaging	High	Low	Direct measure of abdominal subcutaneous adipose tissue	Expensive and time-consuming
VAT (cm²)	Magnetic resonance imaging	High	Low	Direct measure of visceral adipose tissue	Expensive and time-consuming
HTGC (%)	Proton magnetic resonance spectroscopy	High	Low	Direct measure of hepatic fat	Expensive and time-consuming

aSAT, abdominal subcutaneous adipose tissue; BMI, body mass index; HTGC, hepatic triglyceride content; VAT, visceral adipose tissue.

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