Obesity and Cardiovascular disease. Results from the Netherlands Epidemiology of Obesity Study

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CHAPTER 1

General Introduction, Study Population and Outline of this Thesis

GENERAL INTRODUCTION

Obesity is currently a major health problem in developed countries. The global prevalence of obesity has shown a large increase over the past few decades, and this trend also includes the Netherlands [1]. It has been estimated that in 2016 almost half (49.2%) of the adult Dutch population was overweight (body mass index ≥25 kg/m^2) and that 14.2 % of adults had a body mass index of ≥30 kg/m^2, whereas in 1990 the Dutch population included only 33% overweight individuals and 5.5% obese individuals [2]. Obesity has been associated with a wide range of adverse consequences, including cardiovascular disease, type 2 diabetes mellitus and chronic kidney disease [3-5]. The underlying pathophysiology of obesity-related diseases has been extensively studied, but is not completely understood yet. The Netherlands Epidemiology of Obesity study was set up with the aim to investigate pathways that lead to obesity-related diseases. The research of this thesis was performed within the Netherlands Epidemiology of Obesity study, with a focus on the relation of obesity with cardiometabolic and cardiovascular abnormalities.

Obesity is one risk factor for cardiovascular diseases, but many others exist, such as age, sex, genetic factors and environmental factors. Examples of cardiometabolic risk factors are hypertension, dyslipidemia and abnormal glucose metabolism. These cardiometabolic risk factors, together with (abdominal) obesity, tend to cluster or co-occur in individuals. This can lead to the presence of a combination of several cardiometabolic risk factors in an individual, which is called 'metabolic syndrome'. The metabolic syndrome is associated with an increased risk of cardiovascular diseases and type 2 diabetes mellitus [6,7].

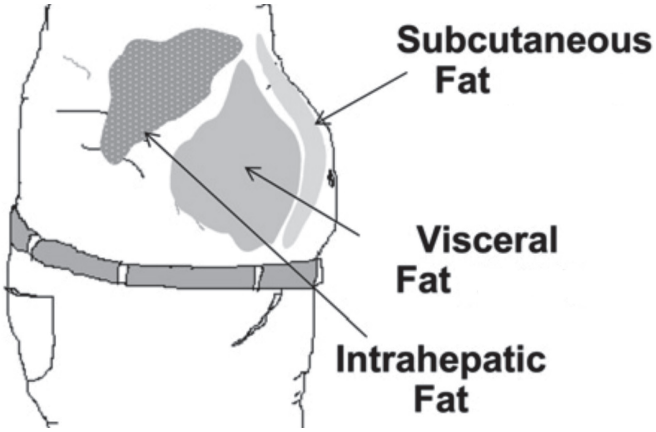

Figure 1. Adapted from Gastaldelli et al [8].

In order to better understand the relations between obesity and its cardiometabolic and cardiovascular consequences, the distribution of the body fat is important. The widely used BMI (kg/m^2) or the percentage of total body fat are measurements of overall adiposity. However, these measures do not take into account the location of the fat. Moreover, an increased body mass index does not necessarily represent a large amount of body fat

mass, but may also represent a large amount of muscle mass. With magnetic resonance imaging, abdominal subcutaneous and visceral adipose tissue can be assessed (Figure 1). Subcutaneous adipose tissue is located underneath the skin, whereas visceral adipose tissue can be found in the abdominal cavity, close to the organs. Other measures are waist circumference as a measure of abdominal adipose tissue, and hip circumference, mostly reflecting gluteofemoral subcutaneous adipose tissue. The ratio of waist circumference to hip circumference, the waist:hip ratio, can also give more information on the distribution of the body fat. With a similar amount of body fat, a higher waist:hip ratio indicates that more fat is located in the abdominal region and a smaller waist:hip ratio indicates more fat in the gluteofemoral region. A body type with a large waist:hip ratio, is often referred to as android or 'apple-shaped' and a body type with a smaller waist:hip ratio is often referred to as gynoid or 'pear-shaped'. The measures of body fat or body fat distribution that will be discussed in this thesis are summarized in Table 1.

Table 1. Measures of body fat or body fat distribution in the Netherlands Epidemiology of Obesity study

Body mass index (kg/m^2)	An individual's weight in proportion to their height squared. Does not distinguish between fat, muscle or bone. Does not provide information on the distribution of body fat
Body fat percentage (%)	The percentage of total body mass that is body fat. A measure of 'overall' adiposity, does not provide information on the distribution of body fat
Waist circumference (cm)	Measurement of 'abdominal' adiposity. Does not distinguish between abdominal visceral and subcutaneous adipose tissue
Waist:hip ratio	The ratio of waist circumference : hip circumference. Measurement of the distribution of body fat
Subcutaneous adipose tissue (cm^2)	Subcutaneous fat (beneath the skin), measured at the level of the 5th lumbar vertebra. Measured in the abdomen, and correlated with measures of overall adiposity [9,10]
Visceral adipose tissue (cm^2)	Intraperitoneal + retroperitoneal fat, measured at the level of the 5th lumbar vertebra. A measure of 'central' or 'abdominal' adiposity

In obesity, excess lipids are stored in several compartments within the human body. Lipids accumulate mainly in subcutaneous adipose tissue, which represents 82-97% of total fat [8]. Lipids can also accumulate in the visceral fat compartment, surrounding the organs, that represents 10-15% of total fat. Furthermore, lipids can be deposited in non-adipose tissue cells, which is referred to as ectopic fat deposition. Ectopic fat accumulates in, among others, the liver (intrahepatic fat), the muscle (intramuscular fat), or the heart. Adipose tissue is not only involved in energy storage, but is also a metabolically active endocrine organ, secreting several adipokines (e.g., leptin, adiponectin and interleukin-6). With the development of obesity, the macrophage content and number of immune cells in the adipocytes increase [11]. Several pro-inflammatory factors, secreted by the adipocytes or macrophages, contribute to the (low-grade) inflammatory state that can be seen with obesity. With increasing

obesity, release of free fatty acids from the hypertrophied adipocytes is also increased and contributes to the adverse metabolic effects that are associated with obesity. Especially the accumulation of visceral adipose tissue has been associated with these cardiometabolic abnormalities and a pro-inflammatory state [12-14]. Another reason why visceral fat is thought to be important for the adverse consequences related to obesity is that free fatty acids released from the visceral adipose tissue flow to the liver, which can lead to hepatic insulin resistance [15]. However, the high amounts of free fatty acids in the systemic circulation of individuals with obesity are mostly originating from non-visceral fat [16,17]. The notion that is gaining support is that accumulation of visceral adipose tissue is a marker of dysfunctionality of the subcutaneous adipose tissue, which leads to ectopic fat deposition, which is referred to as the 'lipid-overflow hypothesis' [18].

Several studies have shown that measures of visceral adipose tissue or abdominal adiposity are important beyond body mass index when assessing the risk of coronary heart disease, as would be expected based on the metabolic abnormalities associated with visceral obesity [19-23]. Cytokines secreted by visceral adipose tissue (e.g., TNF-α, interleukin-6, monocyte chemoattractant protein 1) exert both systemic and local effects. Secreted cytokines increase insulin resistance of adipose tissue and lead to increased adipose tissue vascularization [24,25]. Furthermore, secreted cytokines exert systemic proatherogenic vascular effects, leading to an increased risk of cardiovascular events. For example, plasminogen activator inhibitor-1 (PAI-1), which is produced in visceral adipose tissue at a higher rate than in subcutaneous adipose tissue, appears to increase the risk of atherosclerosis and cardiovascular events [26,27].

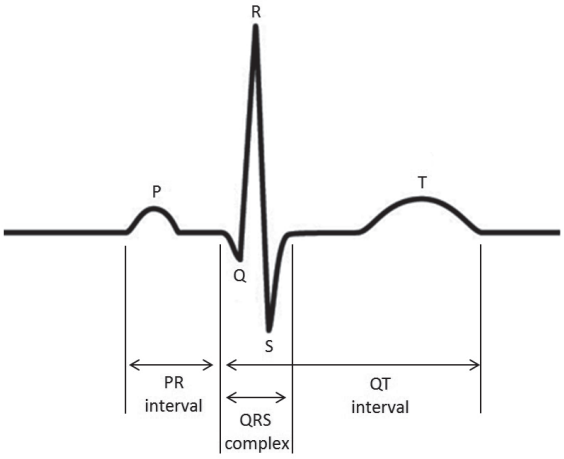

Figure 2. An ECG waveform

Electrocardiography and vectorcardiography

The electrocardiogram provides information for diagnostic and prognostic purposes regarding cardiovascular diseases [28,29]. In this thesis, several aspects of the ECG are assessed, which are shortly presented below. In Figure 2, an example of an ECG waveform is given. The P-wave represents atrial depolarization, while the QRS complex represents ventricular depolarization and the T-wave reflects ventricular repolarization. Furthermore, the direction

of depolarization can be assessed using electrocardiography, with the P wave axis (atria), T wave axis (ventricles) or the QRS axis. Damage to the heart tissue, resulting in altered or absent electrical activity, can be reflected in abnormalities of the electrocardiographic Q-wave. Whether a Q-wave is 'abnormal' depends on several factors, among which its duration, amplitude and the lead in which the Q-wave is observed [30].

Electrocardiography can also be used for the diagnosis of left ventricular hypertrophy, which is associated with adverse cardiovascular outcomes and mortality [31]. Several electrocardiographic criteria for left ventricular hypertrophy exist. However, diagnostic accuracy, and especially the sensitivity, of these criteria is often poor when compared with echocardiography or magnetic resonance imaging [32].

The electrical activity of the heart can also be depicted by vectors with a certain magnitude and direction. In vectorcardiography, the heart vectors are measured using three orthogonal leads, namely X, Y and Z. Then, movement of the heart vector can be pictured three-dimensionally with so-called vector loops. Several vectorcardiography systems have been developed, of which Frank's is best-known [33]. From a regular 12-lead ECG, a Frank vectorcardiogram can be mathematically synthesised by use of matrix multiplication [34-36]. One of the variables that can be assessed by vectorcardiography is the spatial QRS-T angle, which is the angle between the spatial orientation of the QRS-axis and the T-axis, as depicted in Figure 3. With this spatial QRS-T angle, overall heterogeneity of the ventricular action potential morphology can be assessed. A wider spatial QRS-T angle reflects a more heterogeneous (abnormal) repolarization of the ventricles.

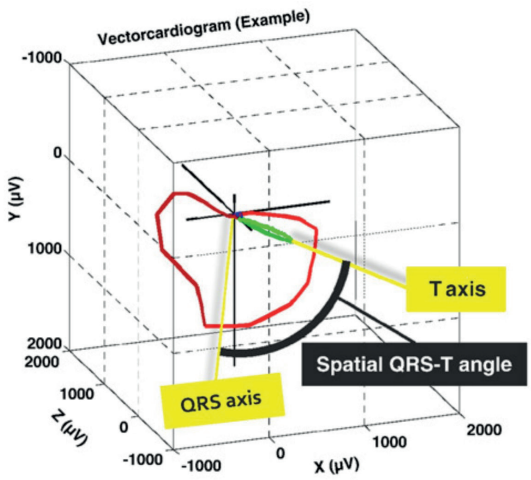

Figure 3. Illustration of the spatial QRS-T angle, adapted from S. Man et al [37].

Study population

The Netherlands Epidemiology of Obesity (NEO) Study is a population-based cohort study including 6671 participants. Participants were recruited from September 2008 till September 2012 in the area of Leiden, via general practitioners, advertisements in local newspapers, posters and registers of three municipalities near Leiden (Leiderdorp, Katwijk and Teylingen). Individuals aged between 45 and 65 years and with a self-reported BMI of ≥27 kg/m^2 were eligible to participate, and in addition, all 45-65 years old inhabitants from Leiderdorp were invited to participate, irrespective of their BMI, to have the full range of BMIs in the study population.

NEO study participants filled out questionnaires on demographic, lifestyle and clinical information. After an overnight fast, participants visited the NEO study center and several measurements were performed. An extensive physical examination was carried out, blood samples were drawn and electrocardiograms were obtained. Furthermore, in a random subgroup of approximately 35% of the study population (without contraindications for magnetic resonance imaging) magnetic resonance imaging of abdominal fat and of pulse wave velocity in the aorta was performed. Also, magnetic resonance imaging of the heart was performed in approximately 15% of the study population. Participants were asked to bring the medication that they used in the month preceding the study visit to the NEO study center. NEO Study participants are followed for the incidence of obesity-related diseases and mortality. However, results in this thesis are based on cross-sectional analyses within the NEO Study.

The Medical Ethics Committee of the Leiden University Medical Center (LUMC) approved the design of the study. All participants gave their written informed consent. Further details of the study design and population can be found in *'The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection'* [38].

Outline of this thesis

Obesity is a well-established risk factor for cardiometabolic diseases. It is thought that the distribution of body fat is important in this relationship, i.e. that abdominal adiposity plays a more important role than overall adiposity in the cardiometabolic consequences associated with obesity. In **Chapter 2**, associations of measures of body fat distribution and cardiometabolic risk factors are investigated within men and women with obesity of the NEO study.

In **Chapter 3**, the associations between the metabolic syndrome and electrocardiographic markers of subclinical cardiovascular disease are investigated in the NEO study. The components of the metabolic syndrome separately, and taken together in the metabolic syndrome definition, are well-established risk factors for cardiovascular diseases [7,39]. This chapter presents, in participants of the NEO study who were free of known cardiovascular diseases, the associations of the metabolic syndrome (absent/present and as metabolic syndrome score) with easily determinable ECG parameters, namely heart rate, P wave duration, QRS duration, PR interval, corrected QT interval, P wave axis, T wave axis, QRS axis and the presence of small abnormal Q-waves. These associations are also investigated for non-obese and obese participants separately.

In **Chapter 4**, associations of overall and abdominal adiposity with easily determinable ECG parameters are presented in NEO study participants who were free of known cardiovascular diseases. Both measures of overall and abdominal adiposity have been associated with cardiovascular endpoints and subclinical cardiovascular disease in the literature [40-44]. We aimed to assess these associations of overall and abdominal adiposity with ECG parameters and also to investigate whether associations of measures of abdominal adiposity were stronger than those of measures of overall adiposity.

An electrocardiogram can show abnormal Q-waves, that can vary in degree of abnormality. Large abnormal Q-waves can, for example, be found on an electrocardiogram of an individual that suffered a myocardial infarction. It is thought that these abnormal Q-waves reflect ischemia, and large abnormal Q-waves therefore are associated with adverse prognosis [45-47]. For borderline abnormal Q-waves this is less clear, especially when there are no other electrocardiographic abnormalities present [48-50]. In **Chapter 5**, the clinical characteristics of participants without abnormal Q-waves and with borderline abnormal Q-waves with or without other electrocardiographic abnormalities are investigated, with a focus on measures of body fat distribution. Furthermore, their associations with subclinical vascular changes are investigated.

In **Chapter 6**, several cardiovascular risk factors associated with a wider spatial QRS-T angle (see Figure 3), are described. We also explored associations between subclinical atherosclerosis (assessed with carotid intima-media thickness) and arterial stiffness (assessed with pulse wave velocity) and the spatial QRS-T angle. Furthermore, we explored the potential added value of the spatial QRS-T angle in cardiovascular risk stratification, as marker of underlying cardiovascular pathology. This was done by determining the ability of the spatial QRS-T angle to discriminate between normal and high carotid intima-media thickness or pulse wave velocity.

As previously described, electrocardiography is widely used in clinical practice, also for diagnostic purposes. Left ventricular hypertrophy, a risk factor for adverse cardiovascular outcomes, can also be diagnosed using an electrocardiogram [31,51]. However, the diagnostic accuracy, especially the sensitivity, for detection of left ventricular hypertrophy with electrocardiography is quite poor compared with the diagnosis assessed with echocardiography or magnetic resonance imaging [32]. Improvement of electrocardiographic criteria for left ventricular hypertrophy is therefore desirable. As is demonstrated in this thesis, several measures of body fat distribution are associated with subclinical cardiovascular changes or increased cardiovascular risk. Addition of measures of body fat distribution to electrocardiogram-based diagnosis could improve their accuracy. For left ventricular hypertrophy, improvement by taking into account body mass index was previously studied [52-55]. However, other measures of body fat distribution were not investigated. In **Chapter 7** improvement of the ECG-based diagnosis of left ventricular hypertrophy, by taking into account measures of body fat distribution, or the extra electrocardiographic parameters T-wave abnormalities and spatial QRS-T angle is presented.

Finally, in **chapter 8** a summary of the results of this thesis, their implications, and directions for future research are provided.

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