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

Elffers, T.W.

# CHAPTER 8

## General discussion

The research within this thesis is focussed on obesity, assessed with several different measures, as well as on cardiometabolic and cardiovascular abnormalities. All research reported in this thesis was performed with baseline data of the Netherlands Epidemiology of Obesity (NEO) study population, and is therefore of cross-sectional nature. Deep phenotyping of participants of this NEO study was performed. Among others, several measures of body fat were determined: next to the more easily obtainable measures like body mass index and waist circumference, abdominal subcutaneous and visceral fat were determined using magnetic resonance imaging in approximately 35% of the study population. Therefore we were able to investigate not just one measure (for example body mass index), but several different measures of body fat and body fat distribution. This is relevant since the functions of adipose tissue and the cardiometabolic consequences of adipose tissue accumulation can differ by the location of the adipose tissue in the human body [1-4]. Cardiac magnetic resonance imaging was also performed in a random subgroup of participants. Chapter 3 through 7 of this thesis encompass variables determined by electrocardiography, which was performed in all participants of the NEO study.

First, we focussed on measures of body fat and its distribution in relation to cardiometabolic risk factors (chapter 2), and the relations of these risk factors with electrocardiographic parameters, also when clustered together in the metabolic syndrome (chapter 3). Then we investigated body fat in relation with electrocardiographic parameters, by studying both measures of overall as well as abdominal adiposity (chapter 4). Chapter 5 and 6 both focus on 'more enhanced' electrocardiographic variables, namely the Q-wave (chapter 5) and the spatial QRS-T angle (chapter 6). In chapter 7 we explored the usefulness of adding measures of body fat or the spatial QRS-T angle to the electrocardiographic criteria for detection of left ventricular hypertrophy.



Below, a summary is given of the main findings of the research described in this thesis and furthermore we describe implications of our research and discuss possible directions for future research.

## MAIN FINDINGS

In chapter 2, associations of measures of body fat and body fat distribution with cardiometabolic risk factors in individuals with obesity are described. The interrelation between adiposity and other cardiometabolic risk factors is reflected in the 'metabolic syndrome'. Metabolic syndrome can be defined by the clustering of at least three out of five (increased waist circumference, high triglyceride levels, low HDL-cholesterol, high blood pressure or high glucose levels) cardiometabolic risk factors in an individual [5] and has previously been associated with cardiovascular disease [6]. Obesity is an important underlying risk factor in the development of the metabolic syndrome. Especially the accumulation of fat in the intra-abdominal region, visceral fat, has been described as a key factor in the link between obesity and several cardiometabolic abnormalities, among which insulin resistance and hypertriglyceridemia [3]. Accumulation of visceral fat is associated with an increased release of free fatty acids into the portal circulation, leading to an increased risk of hepatic insulin resistance [7]. Furthermore, several cytokines are released by visceral fat that promote the development of metabolic disturbances [7]. In chapter 2 we found that

in men and women with obesity, waist:hip ratio, waist circumference and visceral adipose tissue were associated with increased cardiometabolic risk, whereas subcutaneous adipose tissue was not. Visceral adipose tissue, reflecting abdominal adiposity, was most strongly associated with increased cardiometabolic risk.

Electrocardiography is a cheap and also widely used tool in clinical practice for both prognostic and diagnostic purposes, and we investigated in chapter 3 whether individuals with metabolic syndrome but free of known cardiovascular disease, whom we expect to have increased cardiovascular risk, already show subtle differences in electrocardiographic parameters, compared with individuals without the metabolic syndrome. The electrocardiographic parameters that were investigated have previously been associated with an increased risk of several cardiovascular abnormalities [8-15]. As measured by these electrocardiographic parameters, we observed more subclinical cardiovascular disease in individuals with the metabolic syndrome than in individuals without the metabolic syndrome. With every additional metabolic syndrome component more subclinical cardiovascular disease (as assessed with the electrocardiographic parameters) was observed. Stratification by obesity (body mass index ≥ 30 kg/m$^2$) showed similar results for each BMI group. Waist circumference showed the strongest associations with the electrocardiographic parameters.

To further investigate this relation of body fat with electrocardiographic parameters, we investigated both measures of overall as well as of abdominal adiposity in relation with electrocardiographic parameters indicative of subclinical cardiovascular disease in chapter 4 (in individuals without known cardiovascular diseases)**.** In the NEO study, several measures of body fat and distribution have been assessed in a large group of individuals. Therefore, we were able to investigate body mass index, total body fat and subcutaneous adipose tissue as measures of overall adiposity and waist circumference and visceral adipose tissue as measures of abdominal adiposity. We found that both measures of overall as well as of abdominal adiposity were associated with electrocardiographic parameters indicating subclinical cardiovascular disease, which is described in chapter 4. Associations of measures of abdominal adiposity with subclinical disease were not stronger than those of measures of overall adiposity.

The associations of measures of body fat with electrocardiographic parameters indicate potential added value of taking into account measures of body fat in electrocardiography-based diagnoses or in current cardiovascular risk prediction tools. We explored the usefulness of taking into account measures of body fat in the electrocardiographic detection of left ventricular hypertrophy in chapter 7. As previously described, the electrocardiogram is widely used in clinical practice. In chapter 5 and 6 we investigated specific electrocardiographic variables in more detail.

Chapter 5 focuses on the borderline Q-wave, that can be observed on the electrocardiogram. A large abnormal Q-wave is thought to be the results of ischemia and can be present after a myocardial infarction, but also in apparently healthy individuals (silent ischemia) [16]. In clinical practice, a less abnormal, or borderline, Q-wave is often considered as non-pathological, especially in the absence of other electrocardiographic abnormalities (then called an isolated borderline Q-wave). We observed a worse cardiovascular risk profile (i.e.,

higher age, alcohol intake, blood pressure and fasting glucose concentrations) in individuals with isolated borderline Q-waves, than in individuals without abnormal Q-waves. The cardiovascular risk profile was most pathological when the borderline Q-waves was accompanied by other electrocardiographic abnormalities (i.e., non-isolated borderline Q-waves). Several measures of body fat, and especially measures of abdominal adiposity, were higher in individuals with isolated borderline Q-waves and even more so in individuals with non-isolated borderline Q-waves than in individuals without abnormal Q-waves. Furthermore, in individuals with non-isolated Q-waves, pulse wave velocity and carotid intima-media thickness were higher than in individuals without abnormal Q-waves.

In chapter 6 we reported for several cardiovascular risk factors that they are associated with a wider spatial QRS-T angle, which reflects ventricular electrophysiological heterogeneity. This finding was in accordance with previous literature [17-23]. Furthermore, we observed a wider spatial QRS-T angle in individuals with type II diabetes, but also in individuals with high or impaired fasting glucose, compared with individuals with a normal glucose metabolism. We also showed that both carotid intima-media thickness, as measure of subclinical atherosclerosis, and pulse wave velocity, as measure of arterial stiffness, were associated with a wider spatial QRS-T angle. As expected, these associations attenuated after adjustment for cardiovascular risk factors that are plausible common causes of increased carotid intima-media thickness, pulse wave velocity and a wider spatial QRS-T angle.



In chapter 7 we showed that electrocardiographic detection of left ventricular hypertrophy with conventional electrocardiographic criteria could be improved by taking into account body mass index and the extra electrocardiographic parameter spatial QRS-T angle. Left ventricular hypertrophy is associated with increased risk of adverse cardiovascular outcomes and since electrocardiography is low-cost and widely used in clinical practice, improvement of the electrocardiographic detection of left ventricular hypertrophy is desirable. In the NEO study population, all participants underwent electrocardiography, and in a subgroup of participant (approximately 15%) cardiac magnetic resonance imaging was performed. This made it possible to use cardiac magnetic resonance imaging as a reference standard for the determination of left ventricular hypertrophy.

## IMPLICATIONS AND DIRECTIONS FOR FUTURE RESEARCH

In this thesis, we confirmed the importance of visceral obesity in the relation of obesity with cardiometabolic risk factors (chapter 2) and showed that in individuals free of known cardiovascular disease clustering of cardiometabolic risk factors is associated with changes in electrocardiographic parameters indicative of subclinical cardiovascular disease (chapter 3). The findings from chapter 3 also point to the importance of the prevention of these metabolic syndrome components, not only in obese, but also in non-obese individuals. Furthermore, we found that both overall and abdominal adiposity were associated with these deleterious changes in electrocardiographic parameters (chapter 4). Since electrocardiography is an easily assessable, widely used, and relatively cheap tool in clinical practice, it is relevant to explore potential electrocardiographic variables that might be useful in cardiovascular risk prediction or diagnosis, which we did in chapters 5 through 7.

We showed in chapter 5 that borderline Q-waves were associated with a negative cardiovascular risk profile and increased pulse wave velocity and intima-media thickness. These results imply that borderline Q-waves are associated with increased cardiovascular risk and could have prognostic significance for cardiovascular endpoints and thereby might be a useful addition to cardiovascular risk assessment tools. However, it is important to keep in mind that the research from chapter 5 is cross-sectional and longitudinal studies are needed to further investigate the prognostic significance of borderline Q-waves. Two previous studies have shown conflicting results regarding the prognostic significance of borderline Q-waves in Caucasian individuals [24,25]. Also of interest is investigating the relevance of borderline Q-waves within subgroups of individuals with increased cardiovascular risk (e.g., obese individuals), in whom the prevalence of electrocardiographic borderline Q-waves probably is greater. Finally, it may be useful to make a distinction between isolated and non-isolated borderline Q-waves, but in order to do this, a sufficiently large study population is needed. Within the NEO study population only 4.6% of participants showed isolated borderline Q-waves and 1.7% non-isolated borderline Q-waves. Furthermore, when the ability of borderline Q-waves to predict cardiovascular endpoints is investigated, assessing the added value on top of known cardiovascular risk factors is desirable.

Another electrocardiographic variable that might be useful in cardiovascular risk prediction or diagnosis is the spatial QRS-T angle, on which we focus in chapter 6. Our findings suggest that a wider spatial QRS-T angle could be a marker of glucose metabolism impairment or abnormalities associated therewith. Future research is needed to investigate the prognostic value of the spatial QRS-T angle within prediabetic or diabetic individuals and investigate the potential role of the spatial QRS-T angle for risk stratification in these individuals. The associations that we observed between carotid intima-media thickness, pulse wave velocity and the spatial QRS-T angle give more insight into mechanisms that are likely to be involved in spatial QRS-T angle widening. Future longitudinal studies, evaluating the spatial QRS-T angle at different time-points, should aim at further unravelling mechanisms involved in spatial QRS-T angle widening. Our results suggest that the spatial QRS-T angle could be used as a marker of underlying cardiovascular pathology, which is in line with several studies indicating prognostic value of the spatial QRS-T angle for cardiovascular morbidity and mortality [19,22,26-31]. Addition of the spatial QRS-T angle to existing diagnostic tools for cardiovascular diseases should be further investigated.

We have shown that the electrocardiographic detection of left ventricular hypertrophy may be improved by addition of body mass index and the spatial QRS-T angle to conventional electrocardiographic criteria. This improvement of the electrocardiographic detection of left ventricular hypertrophy is relevant in clinical practice, since better electrocardiographic detection prevents unnecessary follow-up investigations by echocardiography or magnetic resonance imaging, which are more expensive tools than electrocardiography. The way to improve the detection of left ventricular hypertrophy that we propose requires little extra effort. Body mass index is often routinely reported and the spatial QRS-T angle can be computed from an electrocardiogram [32]. The usefulness of addition of body mass index to electrocardiographic criteria of left ventricular hypertrophy has been previously reported [33-36], and one study also indicated that the spatial QRS-T angle could be an useful addition [37]. Before implementation of our results in clinical practice, further research is needed. Other

studies are needed to replicate our findings and should preferably be performed in relevant populations, for example individuals visiting the outpatient cardiology clinic.

## NEO FOLLOW-UP

As previously described, the research within this thesis is of a cross-sectional nature and was performed on data of the baseline measurements of the participants of the NEO study. The NEO study was designed as a prospective cohort study. Inclusion of individuals took place from 2008 till 2012 and individuals are now being followed. It is planned that participants of the NEO study will soon return to the study centre for a second visit. Furthermore, information on cardiovascular events and mortality is being collected via among others Dutch general practitioner databases. Several of the directions for future research, as we described above, will become possible when this second visit has taken place and cardiovascular events and mortality have been collected for several years.

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