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

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OBESITY AND CARDIOVASCULAR DISEASE

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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].

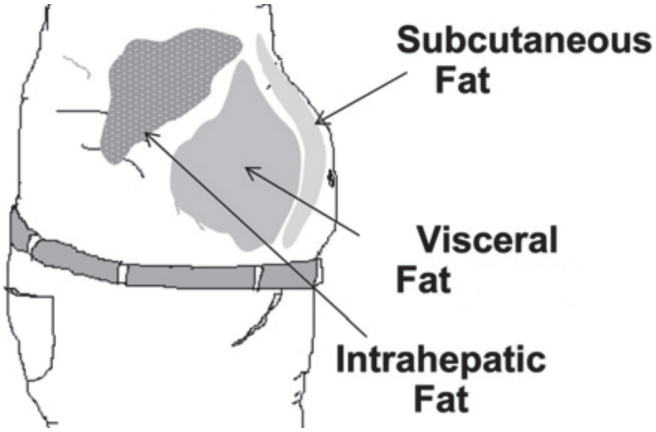

Figure 1. Adapted from Gastaldelli et al [8].

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].

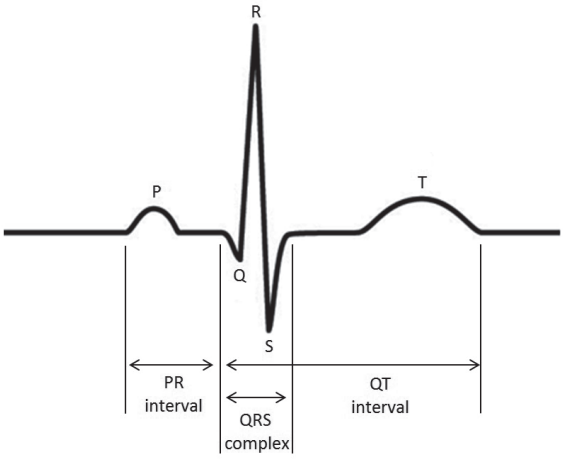

Figure 2. An ECG waveform

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.

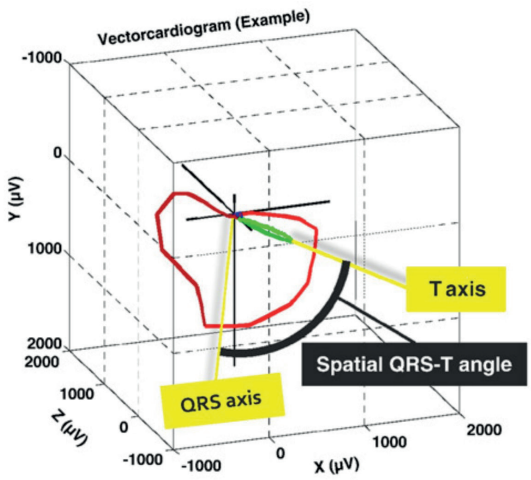

Figure 3. Illustration of the spatial QRS-T angle, adapted from S. Man et al [37].

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.

REFERENCES

1. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. New Engl J Med. 2017;377:13-27.
2. https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/huidige-situatie#node-overgewicht-volwassenen.
3. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet. 2011;377:1085-95.
4. Kovesdy CP, Furth S, Zoccali C. Obesity and kidney disease: hidden consequences of the epidemic. Rev Med Chil. 2017;145:281-91.
5. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PloS one. 2013;8:e65174.
6. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444:881-7.
7. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med. 2006;119:812-9.
8. Gastaldelli A, Basta G. Ectopic fat and cardiovascular disease: what is the link? Nutr Metab Cardiovasc Dis : 2010;20:481-90.
9. Camhi SM, Bray GA, Bouchard C, Greenway FL, Johnson WD, Newton RL, et al. The relationship of waist circumference and BMI to visceral, subcutaneous, and total body fat: sex and race differences. Obesity. 2011;19:402-8.
10. Albulescu D, Iliescu A. Correlations between Areas, Volumes or Body Fat and Anthropometric Variables. Curr Health Sci J. 2014;40:116-8.
11. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112:1796-808.
12. Despres JP. Is visceral obesity the cause of the metabolic syndrome? Ann Med. 2006;38:52-63.
13. Lebovitz HE, Banerji MA. Point: visceral adiposity is causally related to insulin resistance. Diabetes Care. 2005;28:2322-5.
14. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007;116:39-48.
15. Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. Obesity. 2006;14 Suppl 1:16S-9S.
16. Jensen MD. Is visceral fat involved in the pathogenesis of the metabolic syndrome? Human model. Obesity. 2006;14 Suppl 1:20S-4S.
17. Richelsen B, Pedersen SB, Moller-Pedersen T, Bak JF. Regional differences in triglyceride breakdown in human adipose tissue: effects of catecholamines, insulin, and prostaglandin E2. Metabolism. 1991;40:990-6.
18. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev. 2013;93:359-404.
19. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, et al. Abdominal adiposity and coronary heart disease in women. JAMA. 1998;280:1843-8.
20. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 2005;366:1640-9.

21. Dagenais GR, Yi Q, Mann JF, Bosch J, Pogue J, Yusuf S. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. Am Heart J. 2005;149:54-60.
22. Folsom AR, Stevens J, Schreiner PJ, McGovern PG. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. Atherosclerosis Risk in Communities Study Investigators. Am J Epidemiol. 1998;148:1187-94.
23. Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. Br Med J (Clin Res Ed). 1984;289:1257-61.
24. Borst SE. The role of TNF-alpha in insulin resistance. Endocrine. 2004;23:177-82.
25. Schafer K, Konstantinides SV. Update on the cardiovascular risk in obesity: endocrine and paracrine role of the adipose tissue. Hellenic J Cardiol. 2011;52:327-36.
26. Bastelica D, Morange P, Berthet B, Borghi H, Lacroix O, Grino M, et al. Stromal cells are the main plasminogen activator inhibitor-1-producing cells in human fat: evidence of differences between visceral and subcutaneous deposits. Arterioscler Thromb Vasc Biol. 2002;22:173-8.
27. Vaughan DE. PAI-1 and atherothrombosis. J Thromb Haemost. 2005;3:1879-83.
28. Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: The electrocardiogram and its technology: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation. 2007;115:1306-24.
29. Mason JW, Hancock EW, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part II: Electrocardiography diagnostic statement list: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation. 2007;115:1325-32.
30. Prineas RJ CR, Blackburn HW. The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification. J Wright; Boston, MA. 1982.
31. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. Ann Intern Med. 1969;71:89-105.
32. Pewsner D, Juni P, Egger M, Battaglia M, Sundstrom J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. BMJ. 2007;335:711.
33. Frank E. An accurate, clinically practical system for spatial vectorcardiography. Circulation. 1956;13:737-49.
34. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.
35. Levkov CL. Orthogonal electrocardiogram derived from the limb and chest electrodes of the conventional 12-lead system. Med Biol Eng Comput. 1987;25:155-64.
36. Edenbrandt L, Pahlm O. Vectorcardiogram synthesized from a 12-lead ECG: superiority of the inverse Dower matrix. J Electrocardiol. 1988;21:361-7.
37. Man S, Maan AC, Schalij MJ, Swenne CA. Vectorcardiographic diagnostic & prognostic information derived from the 12-lead electrocardiogram: Historical review and clinical perspective. J Electrocardiol. 2015;48:463-75.

38. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013;28:513-23.
39. Esteghamati A, Hafezi-Nejad N, Sheikhbahaei S, Heidari B, Zandieh A, Ebadi M, et al. Risk of coronary heart disease associated with metabolic syndrome and its individual components in Iranian subjects: a matched cohort study. J Clin Lipidol. 2014;8:279-86.
40. Rexrode KM, Buring JE, Manson JE. Abdominal and total adiposity and risk of coronary heart disease in men. Int J Obes Relat Metab Disord. 2001;25:1047-56.
41. Gast KB, den Heijer M, Smit JW, Widya RL, Lamb HJ, de Roos A, et al. Individual contributions of visceral fat and total body fat to subclinical atherosclerosis: The NEO study. Atherosclerosis. 2015;241:547-54.
42. Lear SA, Humphries KH, Kohli S, Frohlich JJ, Birmingham CL, Mancini GB. Visceral adipose tissue, a potential risk factor for carotid atherosclerosis: results of the Multicultural Community Health Assessment Trial (M-CHAT). Stroke. 2007;38:2422-9.
43. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. New Engl J Med. 2008;359:2105-20.
44. Takami R, Takeda N, Hayashi M, Sasaki A, Kawachi S, Yoshino K, et al. Body fatness and fat distribution as predictors of metabolic abnormalities and early carotid atherosclerosis. Diabetes Care. 2001;24:1248-52.
45. Sheifer SE, Gersh BJ, Yanez ND, 3rd, Ades PA, Burke GL, Manolio TA. Prevalence, predisposing factors, and prognosis of clinically unrecognized myocardial infarction in the elderly. J Am Coll Cardiol. 2000;35:119-26.
46. Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, et al. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. JAMA. 2012;308:890-6.
47. Kwong RY, Sattar H, Wu H, Vorobiof G, Gandla V, Steel K, et al. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. Circulation. 2008;118:1011-20.
48. Godsk P, Jensen JS, Abildstrom SZ, Appleyard M, Pedersen S, Mogelvang R. Prognostic significance of electrocardiographic Q-waves in a low-risk population. Europace. 2012;14:1012-7.
49. Li Y, Dawood FZ, Chen H, Jain A, Walsh JA 3rd, Alonso A, et al. Minor isolated Q waves and cardiovascular events in the MESA study. Am J Med. 2013;126:450 e9- e16.
50. Higashiyama A, Hozawa A, Murakami Y, Okamura T, Watanabe M, Nakamura Y, et al. Prognostic value of q wave for cardiovascular death in a 19-year prospective study of the Japanese general population. J Atheroscler Thromb. 2009;16:40-50.
51. Hawkins NM, Wang D, McMurray JJ, Pfeffer MA, Swedberg K, Granger CB, et al. Prevalence and prognostic implications of electrocardiographic left ventricular hypertrophy in heart failure: evidence from the CHARM programme. Heart. 2007;93:59-64.
52. Cuspidi C, Facchetti R, Bombelli M, Sala C, Tadic M, Grassi G, et al. Does QRS Voltage Correction by Body Mass Index Improve the Accuracy of Electrocardiography in Detecting Left Ventricular Hypertrophy and Predicting Cardiovascular Events in a General Population? J Clin Hypertens. 2016;18:415-21.

53. Angeli F, Verdecchia P, Iacobellis G, Reboldi G. Usefulness of QRS voltage correction by body mass index to improve electrocardiographic detection of left ventricular hypertrophy in patients with systemic hypertension. Am J Cardiol. 2014;114:427-32.
54. Robinson C, Woodiwiss AJ, Libhaber CD, Norton GR. Novel Approach to the Detection of Left Ventricular Hypertrophy Using Body Mass Index-Corrected Electrocardiographic Voltage Criteria in a Group of African Ancestry. Clin Cardiol. 2016;39:524-30.
55. Norman JE Jr, Levy D. Adjustment of ECG left ventricular hypertrophy criteria for body mass index and age improves classification accuracy. The effects of hypertension and obesity. J Electrocardiol. 1996;29 Suppl:241-7.

CHAPTER 2

Body fat distribution, in particular visceral fat, is associated with cardiometabolic risk factors in obese women

T.W. Elffers , R. de Mutsert , H.J. Lamb, A. de Roos, K. Willems van Dijk,
F.R. Rosendaal, J.W. Jukema, S. Trompet

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ABSTRACT

Background

Body fat distribution is, next to overall obesity, an important risk factor for cardiometabolic outcomes in the general population. In particular, visceral adipose tissue (VAT) is strongly associated with cardiometabolic risk factors. Since it is unclear whether body fat distribution is also important in men and women with obesity we investigated the associations between measures of body fat distribution and cardiometabolic risk factors in men and women with obesity.

Methods

In this cross-sectional analysis of obese men and women (BMI≥30 kg/m^2) included in the Netherlands Epidemiology of Obesity Study, waist:hip ratio (WHR), waist circumference, and MRI-based abdominal subcutaneous adipose tissue (aSAT) and VAT were determined. Associations between measures of body fat distribution and presence of ≥1 risk factor, such as hypertension or hypertriglyceridemia, were examined using logistic regression analyses; stratified by sex and adjusted for age, ethnicity, education, tobacco smoking, alcohol consumption, physical activity and depending on the association additionally for total body fat or VAT.

Results

We included 2,983 obese individuals (57% women) with a mean age of 56 and standard deviation (SD) of 6 and mean BMI of 34.0 kg/m^2 (4.0), after exclusion of individuals with missing values of cardiometabolic risk factors (n=33). 241 individuals were obese without other cardiometabolic risk factors. In obese women, all measures of body fat distribution except aSAT (OR per SD: 0.76, 95%CI: 0.53, 1.10) were associated with having ≥1 cardiometabolic risk factor, of which VAT most strongly associated (5.77; 3.02, 11.01). In obese men, associations of body fat distribution and the presence of cardiometabolic risk factors were attenuated. (e.g. VAT:1.42; 0.84, 2.41).

Conclusions

In obese women, but less so in men, measures of body fat distribution, of which VAT most strongly, are associated with cardiometabolic risk factors.

INTRODUCTION

Obesity has become a major health problem and in several countries its prevalence keeps rising [1,2]. It has been estimated that obesity was responsible for 3.4 million deaths in 2010 worldwide [3]. Obesity is an important risk factor for the development of cardiovascular diseases (CVD) through cardiometabolic abnormalities such as insulin resistance and hypertension. In addition to overall obesity, body fat distribution, abdominal obesity in particular, has emerged as an important risk factor for type 2 diabetes and CVD in the general population [4,5]. It has been proposed that the excess risk of cardiometabolic disease associated with abdominal obesity is due to the presence of large amounts of visceral adipose tissue (VAT), which is highly metabolically active [6]. Next to insulin resistance, VAT has also been associated with hypertension and subclinical atherosclerosis in the general population [7]. Since body fat distribution is sexually dimorphic and sex hormones may play a role in the adverse effects of VAT, associations of VAT with cardiometabolic risk factors may differ between men and women [8,9].

It is unclear whether these associations of abdominal adiposity with cardiometabolic risk factors are also present in obese individuals. Although obesity is associated with adverse cardiometabolic effects and CVD, not all obese individuals have cardiometabolic abnormalities. It has been suggested that 10-30% of obese individuals do not have obesity-associated cardiometabolic disorders [10-14]. This 'healthy obese' phenotype has been associated with a lower amount of visceral and ectopic fat relative to subcutaneous fat [15-17]. It thus appears that abdominal adiposity, and especially amount of VAT is also important in individuals [18,19]. Therefore, we aimed to investigate the associations between measures of abdominal adiposity with several cardiometabolic risk factors in obese men and women in the NEO Study.

METHODS

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based, prospective cohort study designed to investigate pathways that lead to obesity-related diseases, including 6,671 individuals. Men and women aged between 45 and 65 years with a self-reported BMI of 27 kg/m^2 or higher living in the area of greater 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. Individuals were invited to a baseline visit at NEO study centre of the LUMC after an overnight fast. At the time of inclusion, individuals completed a screening form, asking about anything that might create a health risk or that might interfere with imaging (most notably metallic devices, or claustrophobia). An additional contraindication for magnetic resonance imaging (MRI) was a body circumference of more than 1.70 m. Of the individuals without contra-indications for MRI, approximately 35% were randomly selected to undergo MRI. Prior to the study visit, individuals completed a questionnaire at home with demographic, lifestyle, and clinical information. At the study centre all individuals underwent an extensive physical examination,

including anthropometry and blood sampling. In the present study, individuals without obesity and individuals with missing values of waist circumference, glucose, triglycerides, HDL-cholesterol concentrations, or blood pressure were excluded. Further details of the study design and population have been described in detail elsewhere [20]. The Medical Ethical Committee of the Leiden University Medical Center (LUMC) approved the design of the study and all individuals gave their written informed consent.

Data collection

The ethnicity of individuals was self-identified in eight categories on the questionnaire and then grouped into white and other. Level of education was reported in 10 categories according to the Dutch education system and grouped as low (none, primary school or lower vocational education) versus high education. Tobacco smoking was categorized into current smoker, former smoker, or never smoker. Alcohol consumption was reported using a food frequency questionnaire and calculated into grams/day [21]. Physical activity was reported by the individuals using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) [22]. We calculated the energy expended during physical activity in leisure time in hours per week of metabolic equivalents (MET-h/week). Individuals were asked to bring all the medication they were currently using to the study visit and to report their medical history of diabetes or CVD. Brachial blood pressure was measured in a seated position on the right arm using a validated automatic oscillometric device (OMRON, Model M10-IT, Omron Health Care Inc, IL, USA). Blood pressure was measured three times with 5 minutes rest between consecutive measurements. The mean systolic and diastolic blood pressure were calculated. Blood plasma was sampled after an overnight fast of 10 hours. Fasting glucose, triglyceride and high-density lipoprotein concentrations were measured with standard methods in the central clinical chemistry laboratory of the LUMC [20].

Measures of body fat

Height and weight were measured without shoes and 1 kg was subtracted from the weight to correct for clothing. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Obesity is defined as BMI ≥ 30 kg/m^2. The waist circumference was measured with a horizontally placed flexible tape in the middle of the distance between the lowest rib and the iliac crest. The hip circumference (HC) was measured at the maximum circumference of the buttocks. The waist-hip-ratio (WHR) was calculated by dividing the waist circumference by the HC. With a bio-impedance device (TBF-310, Tanita International Division, UK) total body fat (TBF) was estimated. Abdominal subcutaneous adipose tissue (aSAT) and VAT were assessed by MR imaging (1.5 Tesla MR imaging, Philips Medical Systems) using a turbo spin echo imaging protocol in a subgroup of 2580 individuals. Three transverse images with a slice thickness of 10 mm were obtained during a breath-hold at the level of the fifth lumbar vertebra. The fat depots were converted from the number of pixels to centimeters squared. In the analyses, the average of the three slices was used.

Cardiometabolic risk factors

To define different cardiometabolic risk factors, we used four components of the definition of metabolic syndrome as proposed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII), with minor modifications as stated in the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) statement [23]. We used 1) raised serum triglyceride concentrations (≥1.7 mmol/L) or on drug treatment to reduce triglyceride concentrations; 2) reduced serum HDL-cholesterol concentrations (<1.03 mmol/L for men, <1.3 mmol/L for women) or on drug treatment to elevate HDL-cholesterol; 3) raised blood pressure (≥130 mmHg systolic/≥85 mmHg diastolic) or on antihypertensive drug treatment; 4) raised fasting plasma glucose concentrations (≥5.56 mmol/L) or on drug treatment to lower glucose concentrations.

Statistical analysis

Baseline characteristics are presented as mean (SD), median (interquartile range) or as percentage. We standardized the measures of body fat to a mean of zero with a standard deviation of one. Then we performed logistic regression analyses and calculated odds ratios (ORs) and 95% confidence intervals, per standard deviation of measure of body fat, on having at least one risk factor compared with men and women without any other cardiometabolic risk factors than obesity.

Crude associations were adjusted for sex, age, ethnicity, smoking, alcohol intake, education level, physical activity and statin use. Associations of WHR, waist circumference and VAT were additionally adjusted for total body fat and associations of aSAT were additionally adjusted for VAT. Data were analysed using STATA (Statacorp, College Station, Texas, USA), version 14.

RESULTS

After excluding individuals with missing data on fasting plasma glucose concentrations or glucose lowering therapy (n=26), blood pressure or use of antihypertensive therapy (n=5) and serum triglyceride concentrations or use of medication to reduce triglyceride concentrations (n=2), we ultimately included 2,983 individuals in our analyses of which in 1,071 individuals VAT and aSAT measurements were available. The baseline characteristics are shown in Table 1. Of our study population, 241 individuals did not have any cardiometabolic risk factors and 2,742 individuals had at least one cardiometabolic risk factor. However, 3% of individuals in the group without cardiometabolic risk factors did use lipid lowering medication. Next to 8% participants without any cardiometabolic risk factors, 26% had one risk factor, 34% had two risk factors, 21% had three risk factors and 11% had 4 risk factors. Compared with individuals without any risk factors, individuals with at least one other risk factor were older, more often men, more often former or current smoker and had a higher alcohol intake. There was no difference in physical activity between the groups.

Table 1. Baseline characteristics of the study population

	Cardiometabolic health status	
	0 risk factors (n=241)	≥1 risk factor (n=2,742)
Age, years	53 (6)	56 (6)
Sex, men, %	23	45
Ethnicity, white, (%)	95	94
Smoking		
Never, %	41	32
Former, %	45	53
Current, %	14	16
Alcohol intake, g/day	4.3 (1.0-14.5)	7.8 (1.0-21.7)
Physical activity (MET-hour/week)	24.8 (15.0-42.5)	24.5 (11.1-44.0)
Education level, low, (%)[a]	27	33
History of CVD, %	3	9
BMI, kg/m^2		
Men	32.7 (2.9)	33.3 (3.3)
Women	33.5 (3.3)	34.7 (4.5)
Waist:hip ratio		
Men	0.99 (0.1)	1.02 (0.1)
Women	0.88 (0.1)	0.90 (0.1)
Waist circumference, cm		
Men	112.9 (8.3)	115.2 (9.3)
Women	104.0 (9.1)	107.4 (11.0)
aSAT, cm^2		
Men	360.1 (110.6)	330.3 (87.1)
Women	448.0 (95.4)	432.9 (93.3)
VAT, cm^2		
Men	148.5 (69.6)	180.4 (64.8)
Women	90.0 (30.7)	132.4 (51.2)
Systolic blood pressure, mmHg	116.3 (7.8)	135.7 (16.8)
Diastolic blood pressure, mmHg	76.6 (5.5)	87.2 (10.1)
Use of antihypertensive therapy, %	0	45
Triglycerides, mg/dL	88.6 (67.3-111.6)	130.2 (93.0-176.3)

Table 1. *Continued*

HDL-cholesterol, mg/dL		
Men	51.1 (7.9)	44.7 (10.9)
Women	65.5 (11.4)	56.4 (14.2)
Use of lipid lowering therapy, %	3	21
Fasting glucose, mg/dL	92.8 (5.5)	109.1 (24.0)
Use of glucose lowering therapy, %	0	10

Data are presented as mean (SD), median (25^{th}, 75^{th} percentiles), or percentages. MET, metabolic equivalent of task during leisure time; BMI, body mass index; VAT, visceral adipose tissue; aSAT, abdominal subcutaneous adipose tissue. CVD, cardiovascular disease; HDL, high-density lipoprotein.
[a] lower education: none, primary school, lower vocational education

Table 2 and Figure 1 show ORs and 95% confidence intervals per standard deviation of measure of body fat distribution on having at least one cardiometabolic risk factor in the whole study population and in men and women separately. In the whole study population, one SD higher WHR (0.1) was associated with an OR of 1.40 on having at least one cardiometabolic risk factor compared with individuals without any risk factors (95%CI: 1.15 , 1.70). One SD higher waist circumference (11cm) was associated with an OR of 1.29 (1.05 , 1.59) and one SD higher VAT ($64cm^2$) most strongly with an OR of 2.91 (1.94 , 4.36) on having at least one cardiometabolic risk factor. In the whole study population, no association was found between aSAT and having at least one cardiometabolic risk factor (OR: 0.79; 95%CI: 0.60 , 1.04). Also, there was a clear dose-response between number of cardiometabolic risk factors and measures of body fat distribution, with higher WHR, waist circumference and VAT associated with higher number of risk factors. This was not visible for aSAT. (Data not shown)

In women, 1 SD higher WHR was associated with an OR of 1.45 on having at least one cardiometabolic risk factor compared with individuals without any risk factors (95% CI: 1.17, 1.80), 1 SD higher waist circumference with an OR of 1.29 (1.03, 1.63) and 1 SD higher VAT with an OR of 5.77 (3.02, 11.01). Abdominal SAT was not associated with an OR of 0.76 (0.53, 1.10) per SD on having at least one cardiometabolic risk factor.

In men, the associations of the measures of body fat distribution and cardiometabolic risk factors were much weaker than in women or even absent. In women one SD higher VAT ($64.0\ cm^2$) was associated with an OR of 5.77 (95% CI: 3.02, 11.01) on having at least one cardiometabolic risk factor, while in men one SD higher VAT was associated with an OR of 1.42 (0.84 , 2.41) on having at least one cardiometabolic risk factor. (p-value interaction: 0.002) In men, WHR (OR: 1.21; 95%CI: 0.75, 1.95), waist circumference (1.15; 0.71 , 1.86) and aSAT (0.73; 0.46 , 1.16) were not associated with an increased cardiometabolic risk.

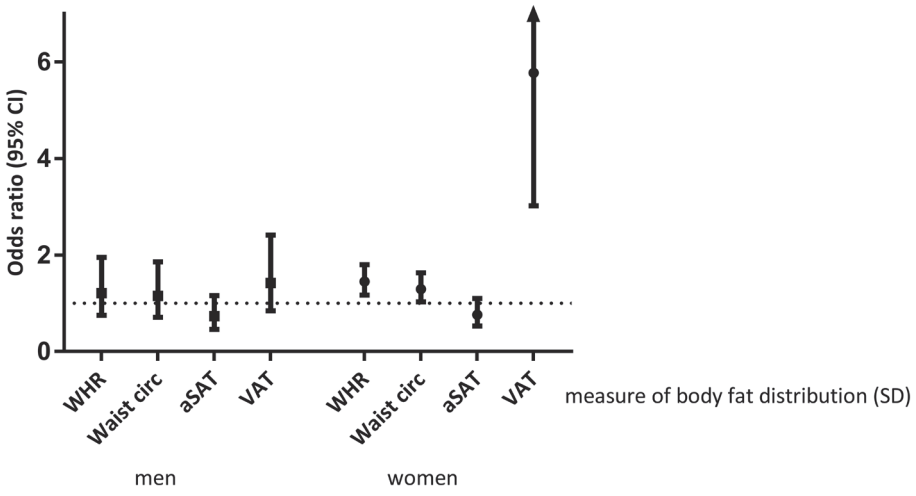

Figure 1. Association of measures of body fat distribution on having at least one cardiometabolic risk factor.

Data are presented as odds ratio (95% CI) per standard deviation of measure of body fat distribution in men and women. WHR, waist:hip ratio; WC, waist circumference; aSAT, abdominal subcutaneous adipose tissue; VAT, visceral adipose tissue adjusted for age, ethnicity, education, tobacco smoking, alcohol consumption and physical activity. Associations of WHR, WC and VAT are additionally adjusted for total body fat and associations of aSAT additionally for VAT.

Table 2. Odds ratios per SD of measures of body fat distribution on having at least one cardiometabolic risk factor

	All		Men		Women		
Fat measure (SD)	Crude	Adjusted[1]	Crude	Adjusted[1]	Crude	Adjusted[1]	p-value int[2]
	n=2,981		n=1,284		n=1,697		
WHR (0.1)	1.79 (1.56, 2.06)	1.40 (1.15, 1.70)	1.76 (1.16, 2.66)	1.21 (0.75, 1.95)	1.58 (1.28, 1.95)	1.45 (1.17, 1.80)	0.380
WC (11 cm)	1.66 (1.43, 1.92)	1.29 (1.05, 1.59)	1.39 (0.96, 2.00)	1.15 (0.71, 1.86)	1.43 (1.20, 1.70)	1.29 (1.03, 1.63)	0.397
	n=1,071		n=536		n=535		
aSAT (105 cm^2)	0.69 (0.56, 0.85)	0.79 (0.60, 1.04)	0.69 (0.45, 1.07)	0.73 (0.46, 1.16)	0.84 (0.63, 1.12)	0.76 (0.53, 1.10)	0.565
VAT (64 cm^2)	3.25 (2.30, 4.58)	2.91 (1.94, 4.36)	1.81 (1.12, 2.94)	1.42 (0.84, 2.41)	5.00 (2.91, 8.60)	5.77 (3.02 , 11.01)	0.002

Data are presented as odds ratio (95% CI) per standard deviation of measure of body fat distribution; WHR, waist:hip ratio; WC, waist circumference; aSAT, abdominal subcutaneous adipose tissue; VAT, visceral adipose tissue.
1: adjusted for age, sex (in all), ethnicity, education, tobacco smoking, alcohol consumption and physical activity. Associations of WHR, WC and VAT are additionally adjusted for total body fat and associations of aSAT additionally for VAT
2: interaction was tested for the adjusted model

DISCUSSION

In this cross-sectional study, we examined several measures of body fat distribution in relation to cardiometabolic risk factors in obese men and women participating in the NEO study. In obese women, WHR, waist circumference and VAT were associated with an increased cardiometabolic risk, whereas aSAT was not. Furthermore, in obese women, VAT was most strongly associated with an increased cardiometabolic risk. In obese men, associations between measures of body fat distribution and cardiometabolic health were much weaker, if present at all. Several studies in the general population have also shown associations of abdominal adiposity, and visceral adiposity in particular, with cardiometabolic risk factors (reviewed in [6]). In the Framingham Heart Study, it was found that also in obese individuals, VAT was associated with hypertension, impaired fasting plasma glucose and the metabolic syndrome [24]. In a study in obese adults, VAT was associated with impaired fasting plasma glucose and type 2 diabetes mellitus, whereas general adiposity was not [25].

VAT could be associated with increased cardiometabolic risk through several mechanisms. VAT is characterised by a high rate of lipolysis, resulting in an excess production of free fatty acids. These free fatty acids are released into the portal circulation and transported to the liver, which could result in excess intra-hepatic fat, a risk factor for cardiometabolic disease [26,27]. In addition, VAT has a high secretion rate of growth factors, cytokines, and hormones that are involved in the pathogenesis of cardiometabolic diseases [28-30]. Furthermore, when adipocytes become larger with an increase in the amount of VAT , they also become more dysfunctional, for example through hypoxia, which leads to the increased release of free fatty acids and cytokines [31].

We observed clear differences in associations of fat distribution and cardiometabolic risk factors between men and women. In obese women, measures of body fat distribution were associated with cardiometabolic health status, while in men they were not or only weakly associated. Differences in associations of measures of body fat distribution and cardiometabolic risk factors between men and women have previously been reported from other studies. In the Framingham Heart Study, in both obese men and women, VAT was associated with hypertension and the metabolic syndrome. The association of VAT with impaired fasting plasma glucose was only present in obese women [24]. A study with older individuals observed that VAT was stronger associated with diabetes in women than in men. However, this study did not investigate obese individuals in particular [32]. Another study of normal-weight individuals observed that VAT was associated with cardiovascular risk factors only in women, but not in men [33]. The exact explanation for these sex differences is to our knowledge not known, but sex steroids likely play a role [8]. Body fat distribution is sexually dimorphic and it is well-known that men accrue more visceral fat and women accrue more subcutaneous fat in general [9]. After the menopause, adipose tissue of women shifts toward the visceral fat depot, likely due to decreasing oestrogen levels [34]. A study with 68 individuals showed that increasing VAT was associated with an increased contribution of VAT lipolysis to hepatic free fatty acid delivery and that this association was stronger in women than in men [35]. Also, some pituitary hormones are known to influence adipocyte function. Prolactin and growth hormone have both been shown to stimulate lipolysis and the effects of growth hormone seem to differ between internal or subcutaneous adipose

tissue sites [36]. Furthermore, it is known that these pituitary hormones can be influenced by sex hormones or have different mRNA levels in men and women [37,38]. Because of their influence on both the distribution and the function of adipose tissue, it is thus likely that sex hormones play an important role in the observed differences between men and women [39,40].

A strength of our study is the large study population (n=2,983) and the extensive phenotyping of the individuals at baseline. Despite the extensive measurements of potential confounding factors in the NEO study, we cannot exclude the possibility of residual confounding. Furthermore, in our study VAT and aSAT were directly assessed by MR imaging. A weakness of this study is that we cannot determine causal relations, because of the observational cross-sectional design. Furthermore, our study population consists mostly of white individuals, and associations between fat depots and cardiometabolic risk factors might differ between ethnic groups. Also, VAT was measured using three transverse slices at the level of the fifth vertebra and then converted to centimetres squared, which does not completely correspond with total VAT volume [41].

In conclusion, our results are in line with previous literature, indicating that abdominal adiposity is an important determinant of cardiometabolic health. On top of previous literature, we showed that in obese women, but less so in obese men, VAT is most strongly associated with cardiometabolic risk factors, compared with the other measures of body fat distribution. Future studies should aim at unravelling the underlying mechanisms of the detrimental metabolic effects of visceral fat in women.

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REFERENCES

1. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants. Lancet. 2011;377:557-67.
2. Stevens GA, Singh GM, Lu Y, Danaei G, Lin JK, Finucane MM, et al. National, regional, and global trends in adult overweight and obesity prevalences. Popul Health Metr. 2012;10:22.
3. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224-60.
4. Lean ME, Han TS, Morrison CE. Waist circumference as a measure for indicating need for weight management. BMJ. 1995;311:158-61.
5. Pouliot MC, Despres JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, et al. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol. 1994;73:460-8.
6. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444:881-7.
7. Chandra A, Neeland IJ, Berry JD, Ayers CR, Rohatgi A, Das SR, et al. The relationship of body mass and fat distribution with incident hypertension: observations from the Dallas Heart Study. J Am Coll Cardiol. 2014;64:997-1002.
8. Palmer BF, Clegg DJ. The sexual dimorphism of obesity. Mol Cell Endocrinol 2015;402:113-9.
9. Blaak E. Gender differences in fat metabolism. Curr Opin Clin Nutr Metab Care. 2001;4:499-502.
10. Karelis AD. To be obese--does it matter if you are metabolically healthy? Nat Rev Endocrinol. 2011;7:699-700.
11. Bluher M. The distinction of metabolically 'healthy' from 'unhealthy' obese individuals. Curr Opin Lipidol. 2010;21:38-43.
12. Karelis AD, St-Pierre DH, Conus F, Rabasa-Lhoret R, Poehlman ET. Metabolic and body composition factors in subgroups of obesity: what do we know? J Clin Endocrinol Metab. 2004;89:2569-75.
13. Marini MA, Succurro E, Frontoni S, Hribal ML, Andreozzi F, Lauro R, et al. Metabolically healthy but obese women have an intermediate cardiovascular risk profile between healthy nonobese women and obese insulin-resistant women. Diabetes care. 2007;30:2145-7.
14. van Vliet-Ostaptchouk JV, Nuotio ML, Slagter SN, Doiron D, Fischer K, Foco L, et al. The prevalence of metabolic syndrome and metabolically healthy obesity in Europe: a collaborative analysis of ten large cohort studies. BMC Endocr Disord. 2014;14:9.
15. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. Diabetes. 1998;47:699-713.
16. Bluher M. Are there still healthy obese patients? Curr Opin Endocrinol Diabetes Obes. 2012;19:341-6.
17. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol. 2013;1:152-62.
18. Primeau V, Coderre L, Karelis AD, Brochu M, Lavoie ME, Messier V, et al. Characterizing the profile of obese patients who are metabolically healthy. Int J Obes. 2011;35:971-81.

19. Boonchaya-anant P, Apovian CM. Metabolically healthy obesity--does it exist? Curr Atheroscler Rep. 2014;16:441.
20. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013;28:513-23.
21. Verkleij-Hagoort AC, de Vries JH, Stegers MP, Lindemans J, Ursem NT, Steegers-Theunissen RP. Validation of the assessment of folate and vitamin B12 intake in women of reproductive age: the method of triads. Eur J Clin Nutr. 2007;61:610-5.
22. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56:1163-9.
23. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735-52.
24. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007;116:39-48.
25. Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. JAMA. 2012;308:1150-9.
26. Rebuffe-Scrive M, Andersson B, Olbe L, Bjorntorp P. Metabolism of adipose tissue in intraabdominal depots of nonobese men and women. Metabolism. 1989;38:453-8.
27. Mauriege P, Galitzky J, Berlan M, Lafontan M. Heterogeneous distribution of beta and alpha-2 adrenoceptor binding sites in human fat cells from various fat deposits: functional consequences. Eur J Clin Invest. 1987;17:156-65.
28. Lemieux I, Pascot A, Prud'homme D, Almeras N, Bogaty P, Nadeau A, et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. Arterioscler Thromb Vasc Biol. 2001;21:961-7.
29. Yatagai T, Nagasaka S, Taniguchi A, Fukushima M, Nakamura T, Kuroe A, et al. Hypoadiponectinemia is associated with visceral fat accumulation and insulin resistance in Japanese men with type 2 diabetes mellitus. Metabolism. 2003;52:1274-8.
30. Miyazawa-Hoshimoto S, Takahashi K, Bujo H, Hashimoto N, Saito Y. Elevated serum vascular endothelial growth factor is associated with visceral fat accumulation in human obese subjects. Diabetologia. 2003;46:1483-8.
31. Trayhurn P. Hypoxia and adipose tissue function and dysfunction in obesity. Physiol Rev. 2013;93:1-21.
32. Kanaya AM, Harris T, Goodpaster BH, Tylavsky F, Cummings SR, Health A, et al. Adipocytokines attenuate the association between visceral adiposity and diabetes in older adults. Diabetes care. 2004;27:1375-80.
33. Tanaka S, Togashi K, Rankinen T, Perusse L, Leon AS, Rao DC, et al. Sex differences in the relationships of abdominal fat to cardiovascular disease risk among normal-weight white subjects. Int J Obes Relat Disord. 2004;28:320-3.
34. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes Relat Disord. 2000;24:226-31.
35. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Invest. 2004;113:1582-8.

36. Flint DJ, Binart N, Boumard S, Kopchick JJ, Kelly P. Developmental aspects of adipose tissue in GH receptor and prolactin receptor gene disrupted mice: site-specific effects upon proliferation, differentiation and hormone sensitivity. J Endocrinol. 2006;191:101-11.
37. Tong YA, Zhao HF, Labrie F, Pelletier G. Ontogeny of prolactin mRNA in the rat pituitary gland as evaluated by in situ hybridization. Mol Cell Endocrinol. 1989;67:11-6.
38. Meinhardt UJ, Ho KK. Modulation of growth hormone action by sex steroids. Clin Endocrinol. 2006;65:413-22.
39. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues - the biology of pear shape. Biol Sex Differ. 2012;3:13.
40. Geer EB, Shen W. Gender differences in insulin resistance, body composition, and energy balance. Gend Med. 2009;6 Suppl 1:60-75.
41. Demerath EW, Shen W, Lee M, Choh AC, Czerwinski SA, Siervogel RM, et al. Approximation of total visceral adipose tissue with a single magnetic resonance image. Am J Clin Nutr. 2007;85:362-8.

CHAPTER 3

Association of metabolic syndrome and electrocardiographic markers of subclinical cardiovascular disease

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ABSTRACT

Background

The metabolic syndrome (MetS) and its components are well-established risk factors for cardiovascular diseases (CVD). It is inconclusive whether MetS and MetS score are associated with electrocardiographic markers of subclinical CVD, therefore we investigated this in a population without pre-existing CVD.

Methods

We performed a cross-sectional analysis in the Netherlands Epidemiology of Obesity study, a population-based cohort including 6671 participants aged 45-65. We excluded participants with pre-existing CVD (n=499) or missing MetS components (n=58). MetS was defined based on a modified definition of Adult Treatment Panel III. Subclinical CVD parameters were determined with 12-lead ECGs. MetS score was defined as number of abnormal MetS components and obesity as Body Mass Index (BMI) ≥30 kg/m^2. We performed weighted adjusted linear regression analyses.

Results

Our study population (n=6114) had a mean (SD) BMI of 26.3 (4.4) kg/m^2 and MetS was present in 24% of participants. All ECG parameters differed between participants with and without MetS. Per additional MetS component, heart rate was 0.17 SD (95%CI:0.15, 0.19) higher, P wave duration, QRS complex duration and corrected QT interval were longer (0.07 SD (0.05, 0.10), 0.04 SD (0.01, 0.06) and 0.05 SD (0.02, 0.08) respectively), P wave axis, T wave axis and QRS axis were lower (-0.10 SD (-0.12, -0.07), -0.07 SD (-0.10, -0.05) and -0.19 SD (-0.22, -0.16)) and percentage small Q-waves also increased per additional MetS component. Associations were stronger in non-obese than obese participants. In joint modelling of all MetS components, increased waist circumference showed strongest associations with ECG parameters.

Conclusions

MetS score and its individual components, in particular abdominal obesity, are associated with ECG markers of subclinical CVD, showing the importance of limiting the amount of MetS components in both obese and non-obese persons.

INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death worldwide [1]. Metabolic syndrome (MetS) is a combination of cardiovascular risk factors such as obesity, hyperglycemia, dyslipidemia and hypertension, and has been associated with increased risk of CVD. A recent meta-analysis showed that individuals with MetS had a two-fold increased risk of CVD and a 1.5-fold increased risk of all-cause mortality [2]. In a study including 4122 participants with a mean follow-up of 8.5 years, the risk of coronary heart disease increased with increasing number of MetS components [3]. In addition, there are also studies showing that separate components are more important for the risk of different outcomes than the combination of components in MetS [4,5]. Obesity is a key component in MetS, becoming more relevant because of its increasing prevalence. However, there are also people who are metabolically unhealthy, but non-obese. Also, in these individuals there is a higher prevalence of diabetes and CVD [6]. Therefore it is important to understand the relation between MetS and its components and subclinical CVD in both non-obese and obese subpopulations.

Some previous studies investigated the association between MetS and subclinical CVD. Presence of MetS was associated with increased arterial stiffness, higher resting heart rate, prolonged QRS and prolonged QT interval and an abnormal T-wave axis [7,8]. However, associations of MetS with subtle changes in electrocardiographic markers, indicative of subclinical CVD, are not fully elucidated. Few studies investigated these associations in both non-obese and obese subpopulations. Knowledge on these associations may give more insight in possible population consequences of subtle ECG changes. Therefore, our objectives were to investigate the associations of MetS with subclinical CVD, of the number of abnormal MetS components with subclinical CVD and to investigate whether these associations differ between obese and non-obese individuals without pre-existing CVD within the Netherlands Epidemiology of Obesity (NEO) study. Furthermore, we investigated contributions of separate MetS components to subclinical CVD.

METHODS

Study design and population

The NEO study is a population-based, prospective cohort study comprising 6671 individuals, included between 2008 and 2012 and aged between 45 and 65 years [9]. Participants with BMI of 27 kg/m^2 or higher were oversampled and also 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. Participants were invited to a baseline visit at the NEO study centre of the Leiden University Medical Center (LUMC) after an overnight fast. During this visit all participants underwent an extensive physical examination, including blood sampling and ECG. Participants completed a questionnaire with demographic, lifestyle, and clinical information. We excluded participants with missing values of waist circumference, glucose, triglycerides, HDL-cholesterol or blood pressure. Furthermore, participants with pre-existing CVD, defined as myocardial infarction, angina, congestive heart failure, stroke, or peripheral vascular disease, were excluded. The Medical Ethical Committee of the LUMC approved the design of the study. All participants gave informed consent.

Data collection

Ethnicity was reported by the participants in eight categories and grouped into white and other. Level of education was reported in 10 categories according to the Dutch education system and grouped as low (none, primary school or lower vocational education) versus high. Tobacco smoking was categorized into current, former, or never smoker. Alcohol consumption was reported using a food frequency questionnaire and calculated into grams/day. Physical activity was reported using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) questionnaire [10]. Energy expended during physical activity was calculated in leisure time in hours per week of metabolic equivalents (MET-h/week). Participants were asked to bring the medication they were currently using to the study visit and to report their medical history of diabetes or CVD. Height and weight were measured without shoes and 1 kg was subtracted from the weight to correct for clothing. BMI was calculated by dividing weight in kilograms by height in meters squared. Waist circumference was measured with a horizontally placed flexible tape in the middle of the distance between the lowest rib and the iliac crest. Brachial blood pressure was measured in seated position on the right arm using a validated automatic oscillometric device (OMRON, Model M10-IT, Omron Health Care Inc, IL, USA). Blood pressure was measured three times with 5 minutes rest between consecutive measurements. Mean systolic and diastolic blood pressure were calculated. Blood plasma was sampled after an overnight fast of 10 hours. Fasting glucose, triglyceride and high-density lipoprotein concentrations were measured with the enzymatic colorimetric method (Roche Modular Analytics P800, Roche Diagnostics Mannheim, Germany).

A 12-lead ECG was obtained using a Mortara Eli-350 electrocardiograph (Mortara Instrument Inc., Best, the Netherlands) after a resting period of at least 10 minutes. ECGs were analysed using the automatic MATLAB-based (The MathWorks, Natick, MA) program BEATS and the semiautomatic program LEADS [11,12]. ECGs were also provided to the University of Glascow ECG core lab where Minnesota Codes were determined [13-15]. In order to assess subtle changes in ECG parameters, that could indicate subclinical CVD in a population without known overt cardiovascular diseases, heart rate, P wave duration, QRS complex duration, PR interval, corrected QT interval (corrected according to the Bazett formula), P-, T- and QRS axis were determined. Furthermore, small Q-waves were assessed using the Minnesota Coding System, which is a system to objectively describe electrocardiographic findings. We defined small Q-waves as Minnesota Codes 1.2.x or 1.3.x.

These ECG parameters are known to be of prognostic importance for CVD development [16-19].

Metabolic syndrome definition

The definition of MetS as proposed by the National Cholesterol Education Program Adult Treatment Panel III was used, with minor modifications as stated in the American Heart Association and the National Heart, Lung, and Blood Institute statement [20]. MetS is defined as the presence in an individual of at least three out of the five following criteria: 1)increased waist circumference (>102 cm for men, >88 cm for women); 2)raised serum triglyceride levels (1.7 mmol/L) or on drug treatment to reduce triglyceride concentrations; 3)reduced serum HDL-cholesterol levels (1.03 mmol/L for men, 1.3 mmol/L for women) or on drug

treatment to elevate HDL-cholesterol; 4)raised blood pressure (≥130 mmHg systolic/≥85 mmHg diastolic) or on antihypertensive drug treatment; 5)raised fasting plasma glucose (5.56 mmol/L) or on drug treatment to lower glucose concentrations. Obesity is defined as BMI ≥ 30 kg/m^2 and MetS score as total number of MetS components present in an individual.

Statistical analysis

To correctly represent associations in the general population, adjustments for the oversampling of participants with BMI of 27 kg/m^2 or higher were made by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality whose BMI distribution was similar to that of the general Dutch population [21, 22].

Baseline characteristics were summarized as mean (SD) or percentage and stratified by the presence of MetS. We examined the associations between MetS and the ECG parameters heart rate (bpm), P wave duration (ms), QRS complex duration (ms), PR interval (ms), corrected QT interval (ms), P- (◦), T- (◦), QRS axis (◦) and percentage of small Q-waves using linear regression analysis.

We calculated Z-scores and standardized the ECG parameters to a mean of zero with a standard deviation of one, in order to express the associations in SDs and compare them with each other. Next, we performed linear regression analyses with MetS score (0-5) as the independent and standardized ECG parameters as the outcome variables. To investigate differences in associations between obese and non-obese persons, we tested for interaction with obesity by including product terms of obesity and MetS in all models. Finally, to investigate the separate contributions of the MetS components in relation to the ECG parameters, we included all MetS components (dichotomous) in one joint model. Crude associations were adjusted for age, sex, ethnicity, smoking, alcohol intake, education level, physical activity, and statin use. Data were analysed using STATA version 14.

RESULTS

Of the 6671 participants included in the NEO study, we consecutively excluded participants with a history of CVD (n=499), missing data on fasting plasma glucose or glucose lowering therapy (n=45), blood pressure or use of antihypertensive therapy (n=7), waist circumference (n=4) and serum triglycerides or use of medication to reduce triglyceride concentrations (n=2). We ultimately included 6114 participants. Baseline characteristics are shown in Table 1. Of the participants, 24% met MetS criteria. Participants with MetS were more often men, current or former smoker and had a lower educational level. By definition, all other cardiovascular risk factors were more often present in the participants with MetS.

Table 1. Baseline characteristics of NEO study population without pre-existing CVD

	Metabolic syndrome	
	No (76%)	Yes (24%)
Age, years	55.3 (5.2)	56.5 (7.9)
Sex, men, %	39.9	52.6
Ethnicity, white, *%*	95	96
BMI, kg/m^2	25.0 (3.0)	30.1 (6.4)
Smoking, %		
Never	40.8	33.5
Former	44.3	48.0
Current	14.9	18.5
Alcohol intake, g/dag	9.7 (3.2-20.9)	10.4 (2.0-24.6)
Physical activity, MET-hour/week	30.9 (16.9-51.0)	25.8 (11.8-45.2)
Education level, low, (%)*	16.0	28.0
Fasting plasma glucose, mg/dL	93.7 (88.3-98.9)	105.7 (98.9-114.2)
Use of glucose lowering therapy, *%*	0.6	7.6
Systolic blood pressure (mmHg)	127.6 (14.1)	137.6 (22.6)
Diastolic blood pressure (mmHg)	81.7 (8.5)	87.9 (13.4)
Use of antihypertensive therapy, *%*	14.5	40.3
Waist circumference (cm)		
Men	94.4 (7.7)	106.9 (13.9)
Women	83.6 (9.0)	101.1 (15.4)
Triglycerides, mg/dL	78.8 (59.3-106.3)	160.3 (111.6-208.1)
HDL, mg/dL		
Men	55.8 (11.0)	43.3 (15.4)
Women	71.5 (13.9)	53.4 (18.8)
Use of lipid lowering therapy, %	4.8	18.8

Data are presented as mean (SD), median (IQR) or percentage. Results were based on analyses weighted towards the BMI distribution of the general population.
BMI, body mass index; MET, metabolic equivalent of task
* lower education: none, primary school, lower vocational education

Table 2. Differences in baseline ECG parameters between non-obese and obese participants with and without metabolic syndrome

	Non-obese (84%)			Obese (16%)			
ECG parameter	No MetS (83%)	MetS (17%)	Diff (95%CI)	No Mets (36%)	MetS (64%)	Diff (95%CI)	p-value int
Heart rate (bpm)	62.4 (0.2)	67. 7 (0.5)	5.0 (3.9 , 6.2)	65.8 (0.3)	68.8 (0.3)	3.1 (2.2 , 4.0)	0.006
P duration (ms)	110.9 (0.4)	114.3 (0.6)	2.3 (0.9 , 3.6)	115.2 (0.5)	115.8 (0.4)	-0.6 (-1.8 , 0.6)	0.002
QRS duration (ms)	92.3 (0.3)	94.5 (0.5)	0.8 (-0.4 , 2.0)	92.9 (0.4)	95.0 (0.3)	0.7 (-0.3 , 1.7)	0.985
PR interval (ms)	162.1 (0.6)	166.3 (1.0)	2.4 (-0.1 , 4.8)	163.9 (0.8)	164.8 (0.6)	-1.1 (-3.0 , 0.9)	0.029
QTc interval (ms)	413.7 (0.6)	414.7 (1.0)	1.2 (-1.0 , 3.4)	416.1 (0.9)	418.2 (0.6)	2.2 (0.2 , 4.2)	0.373
P axis (°)	49.0 (0.7)	44.2 (1.0)	-4.3 (-6.8 , -1.9)	40.4 (0.8)	40.6 (0.6)	-0.2 (-2.3 , 1.9)	0.001
T axis (°)	39.4 (0.6)	36.2 (1.1)	-2.8 (-5.5 , -0.1)	32.3 (0.8)	34.4 (0.7)	2.0 (-0.2 , 4.2)	0.001
QRS axis (°)	39.8 (0.8)	23.0 (1.4)	-13.3 (-16.6 , -10.1)	23.2 (1.0)	18.4 (0.8)	-2.9 (-5.3 , -0.5)	<0.001
Small Q-wave (%)	5.2	9.1	2.8 (0.2 , 5.4)	8.1	9.3	0.7 (-1.7 , 3.0)	0.121

Data are presented as mean (se) or percentage.
Results were based on weighted linear regression analysis adjusted for age, sex, ethnicity, smoking, alcohol intake, education level, physical activity and statin use.
MetS, metabolic syndrome.

Crude and adjusted weighted linear regression analyses were performed to compare ECG parameters between participants with and without MetS. Participants with MetS had higher values of heart rate, P wave duration, QRS complex duration, PR interval and corrected QT interval, and lower values of P, T and QRS axis, i.e. more superiorly oriented axes. Furthermore, small Q-waves were more often present in participants with MetS (Supplementary Table 1). Table 2 shows this analysis for the non-obese and obese participants separately. In the non-obese population, heart rate (difference: 5.0 bpm; 95%CI: 3.9, 6.2), P wave duration (2.3 ms; 0.9, 3.6), P axis (-4.3°; -6.8, -1.9), T axis (-2.8°; -5.5, -0.1), QRS axis (-13.3°; -16.6, -10.1) and small Q-waves (2.8%; 0.2, 5.4) differed between participants with and without MetS and in the obese population, there were differences in heart rate (3.1 bpm; 2.2, 4.0), corrected QT interval (2.2 ms; 0.2, 4.2) and QRS axis (-2.9°; -5.3, -0.5).

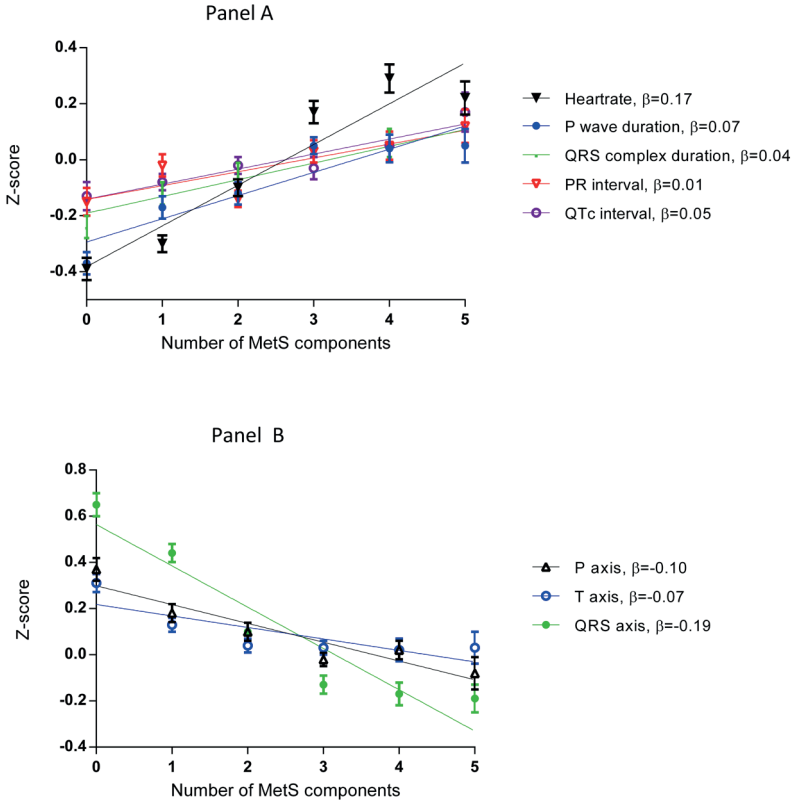

Figure 1. ECG parameters in relation to metabolic syndrome score.
Regression lines are shown for the different ECG parameters. ECG parameters are expressed in Z-scores. **a**. ECG parameters that increased with increasing number of metabolic syndrome components; **b**. ECG parameters that decreased with increasing number of metabolic syndrome components. Results were based on weighted analysis adjusted for age, sex, ethnicity, smoking, alcohol intake, education level, physical activity and statin use

Figure 1 displays regression lines per SD of the ECG parameters used in a linear regression analysis per MetS component, with panel A showing all ECG parameters that increased and panel B showing all ECG parameters that decreased with increasing number of components. Per additional MetS component, heart rate, P wave duration, QRS complex duration and QTc interval increased and P-, T- and QRS axis decreased.

In Table 3, the association of MetS score, ranging from zero to five, with Z-scores of ECG parameters is shown for obese and non-obese participants separately. For P wave duration (p=0.027), P axis (p=0.001), T axis (p<0.001) and QRS axis (p<0.001) the interaction terms between MetS score and obesity were statistically significant. In the non-obese participants, with each additional MetS component, P wave duration was 0.05 SD (95%CI: 0.02,0.09) longer, P axis was 0.08 SD (0.05,0.12) lower, T axis was 0.07 SD (0.04,0.11) lower and QRS axis was 0.17 SD (0.13,0.21) lower. In the obese participants, P wave duration, P axis and T axis were not associated with increasing amount of MetS components, whereas QRS axis was 0.05 SD (0.02,0.08) lower with each additional component, but this was less than in the non-obese participants. Furthermore, in non-obese participants percentage small Q-waves increased with each additional MetS component (4.5; 4.7; 6.8; 7.5; 11.6; 12.3%), while this was less clear in obese participants (0; 6.1; 8.8; 9.6; 9.2; 8.3%).

Table 3. Relation of standardized ECG parameters to metabolic syndrome scores (range 0-5)

ECG parameter	All	non-obese (84%)	obese (16%)	p-value int
Heart rate	0.17 (0.15 , 0.19)	0.16 (0.13 , 0.19)	0.12 (0.09 , 0.16)	0.137
P duration	0.07 (0.05 , 0.10)	0.05 (0.02 , 0.09)	0.00 (-0.04 , 0.03)	0.027
QRS duration	0.04 (0.01 , 0.06)	0.02 (-0.01 , 0.06)	0.04 (0.00 , 0.07)	0.466
PR interval	0.01 (-0.02 , 0.04)	0.00 (-0.04 , 0.04)	0.01 (-0.03 , 0.04)	0.866
QTc interval	0.05 (0.02 , 0.08)	0.04 (0.00 , 0.07)	0.05 (0.01 , 0.09)	0.335
P axis	-0.10 (-0.12 , -0.07)	-0.08 (-0.12 , -0.05)	-0.01 (-0.05 , 0.02)	0.001
T axis	-0.07 (-0.10 , -0.05)	-0.07 (-0.11 , -0.04)	0.04 (0.00 , 0.08)	<0.001
QRS axis	-0.19 (-0.22 , -0.16)	-0.17 (-0.21 , -0.13)	-0.05 (-0.08 , -0.02)	<0.001

Data are presented as β (95%CI); change in Z-score of ECG parameter per metabolic syndrome component. Results were based on weighted analysis. Multivariate model adjusted for age, sex, ethnicity, smoking, alcohol intake, education level, physical activity and statin use.

Table 4. Influence of metabolic syndrome components on ECG parameters

ECG parameter	waist circumference	triglycerides	HDL-cholesterol	blood pressure	fasting glucose
Heart rate (bpm)	2.4 (1.6 , 3.2)	3.2 (2.2 , 4.1)	-0.3 (-1.2 , 0.7)	1.8 (1.1 , 2.5)	2.2 (1.4 , 3.1)
P duration (ms)	3.4 (2.3 , 4.4)	-0.6 (-1.9 , 0.7)	1.7 (0.3 , 3.0)	1.1 (0.0 , 2.2)	-0.8 (-2.0 , 0.4)
QRS duration (ms)	1.0 (0.1 , 1.9)	-0.5(-1.5 , 0.6)	0.2 (-0.8 , 1.2)	1.4 (0.4 , 2.4)	-0.1 (-1.1 , 1.0)
PR interval (ms)	2.4 (0.6 , 4.3)	-1.5 (-3.9 , 0.8)	3.6 (1.2 , 6.1)	0.4 (-1.6 , 2.5)	-3.5 (-5.4 , -1.6)
QTc interval (ms)	2.7 (1.0 , 4.3)	0.1 (-2.0 , 2.1)	1.8 (-0.1 , 3.8)	1.9 (0.2 , 3.7)	-0.9 (-2.7 , 1.0)
P axis (°)	-7.4 (-9.4 , -5.3)	-0.6 (-2.9 , 1.6)	-2.0 (-4.6 , 0.6)	-1.9 (-4.1 , 0.2)	1.0 (-1.3 , 3.2)
T axis (°)	-5.2 (-7.1 , -3.3)	-0.2 (-2.5 , 2.2)	-2.0 (-4.4 , 0.4)	-2.7 (-4.7 , -0.8)	1.2 (-0.8 , 3.2)
QRS axis (°)	-12.9 (-15.2 , -10.5)	-2.5 (-5.5 , 0.5)	-4.5 (-7.7 , -1.4)	-5.6 (-8.2 , -3.0)	-2.7 (-5.4 , 0.0)
Small Q-wave (%)	1.9 (0.2 , 3.6)	1.6 (-0.7 , 3.9)	0.7 (-1.7 , 3.2)	1.0 (-0.8 , 2.8)	0.4 (-1.6 , 2.3)

Data are presented as β(95%CI). Results were based on weighted analysis.
Multivariate model adjusted for age, sex, ethnicity, smoking, alcohol intake, education level, physical activity, statin use and the other MetS components.

In a joint model including all separate MetS components together with potential confounding factors (Table 4), high waist circumference was associated with all ECG parameters. High waist circumference was associated with 2.4 bpm (95%CI; 1.6, 3.2) higher heart rate, 3.4 ms (2.2, 4.4) longer P wave duration, 1.0 ms (0.1, 1.9) longer QRS complex duration, 2.4 ms (0.6, 4.3) longer PR interval, 2.7 ms (1.0, 4.3) longer corrected QT interval, 7.4° (5.3, 9.4) lower P axis, 5.2° (3.3, 7.1) lower T axis, 12.9° (10.5, 15.2) lower QRS axis and 1.9% (0.2, 3.6) more small Q-waves. In this joint model, hypertriglyceridemia was only associated with heart rate, reduced serum HDL-cholesterol with P wave duration, PR interval and QRS axis, increased blood pressure with heart rate, P wave duration, QRS complex duration, corrected QT interval, T axis and QRS axis and hyperglycemia with heart rate and PR interval.

DISCUSSION

We observed that electrocardiographic markers of subclinical CVD differed between participants with and without MetS, indicating more subclinical CVD in participants with than without MetS. ECG parameters associated with subclinical CVD increased with every additional MetS component present in an individual and for P wave duration, P axis, T axis and QRS axis, these associations were stronger in the non-obese than the obese population. Furthermore, in joint models including all MetS components high waist circumference was associated with all ECG parameters whereas results for the other components were less strong.

In this study, subclinical CVD was investigated by looking at subtle changes in ECG parameters. Although the observed changes are small and not per se of direct prognostic significance on the individual level, they give more insight on a population level. All ECG parameters investigated, have previously been associated with a broad range of future cardiovascular abnormalities, events or mortality [16-18, 23-27].

Differences between participants with and without MetS have also been demonstrated in other studies. In a study with 6765 participants aged 45-84 years, MetS was associated with ECG abnormalities [28]. The association of MetS with higher heartrate and also lower heart rate variability, indicative of an adverse effect of MetS on the cardiac autonomic modulation has previously been reported in literature [29,30]. Furthermore MetS has been associated with borderline or abnormal T axis [31]. Furthermore, in a study that included both individuals with MetS as well as their offspring, evidence of early subclinical cardiovascular damage was found in individuals with MetS as well as their offspring [32]. In our study associations between MetS and ECG parameters are confirmed in a large group of extensively phenotyped individuals and on top of that we showed that it is important to pay attention to asymptomatic patients, with just zero or one component present, to prevent the increase of MetS components in these individuals and thereby also the development of CVD. We showed that this is already important in the non-obese population, since the associations of MetS with subclinical CVD are also present in this population.

We observed associations between the presence of MetS and also MetS score and ECG parameters. Thus far, literature is inconclusive about the risk associated with MetS components and increasing MetS score. In a study with 9406 participants, it was concluded that MetS was not associated with 1-year mortality, while reduced HDL-cholesterol was associated with higher risk and raised triglycerides were associated with lower 1-year mortality risk [5]. In a case-control study, MetS was associated with higher risk of venous thromboembolism. However, after multivariate analysis, only abdominal obesity was associated with higher risk [4]. There are also studies stating that increasing MetS score can be used as a risk factor for CVD [33, 34]. Moreover, it was shown that MetS is associated with increased heart failure risk in individuals without diabetes or baseline macrovascular complications [35].

Associations between ECG parameters and MetS score seemed stronger in the non-obese population. A possible explanation is that obese participants are more likely to have a high waist circumference and also worse ECG parameters, so they have less variation in their MetS score which varies from zero to five. Nevertheless, our study shows that in non-obese participants every additional component contributes to the association with subclinical CVD. However, pathophysiological mechanisms underlying this difference between non-obese and obese participants remain unclear from existing literature.

Furthermore, in the analysis of MetS components separately (Table 4), we are aware that when adjusting the associations of increased waist circumference and subclinical CVD, it is possible that adjustments are made for factors that might partially be in the causal pathway. However, this would dilute the associations, so the true association between increased waist circumference and subclinical CVD might even be stronger than the association that we find.

It is inconclusive through which mechanisms obesity or increased waist circumference lead to ECG abnormalities. Possibilities are increased sympathetic system activity, elevation of the diaphragm and increased cardiac output leading to left ventricular hypertrophy [36,37]. Body fat was associated with measures of sympathetic activation in subjects with structurally normal hearts in the NEO study [38]. The leftward (superior) shifts of the T-, P- and QRS axis were associated with obesity in other studies [39-41]. Obesity can lead to an increase in cardiac loading and remodelling of the heart muscle leading to PR interval lengthening [42]. Also hormones produced by the adipose tissue influence the myocardial matrix, resulting in electrophysiological remodelling [42]. Also endovascular effects of obesity are present, induced by paracrine hormone expression of the adipose tissue that could alter the atrial function [43].

A strength of this study is the large study population (n=6114) and the extensive measurements of potential confounding factors that were performed in the NEO study. A weakness is its observational cross-sectional design, precluding any conclusions about causality of the observed relationships.

On the basis of its observed relation with ECG parameters, we conclude that MetS is associated with subtle changes in ECG parameters, indicative of more subclinical CVD. As these ECG parameters are predictive of CVD and MetS score was associated with higher values of these parameters, MetS could be used as an early marker for subclinical CVD risk stratification, and to manage risks already in an early disease state. Furthermore, prevention of the development of MetS components is important in obese, but also very relevant in non-obese individuals.

Conclusions

Metabolic syndrome score and its individual components, in particular abdominal obesity, are associated with ECG markers of subclinical CVD in both obese and non-obese persons.

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Supplementary Table1 . Differences in baseline ECG parameters between participants with and without metabolic syndrome

	Metabolic syndrome			
ECG parameter	No (76%)	Yes (24%)	Diff (95%CI)	Diff (95%CI)[1]
Heart rate (bpm)	62.6 (0.2)	68.1 (0.3)	5.5 (4.7 , 6.2)	5.2 (4.4 , 6.0)
P duration (ms)	111.2 (0.3)	114.9 (0.4)	3.7 (2.8 , 4.7)	2.8 (1.8 , 3.7)
QRS duration (ms)	92.5 (0.3)	94.6 (0.3)	2.1 (1.3 , 3.0)	1.2 (0.3 , 2.1)
PR interval (ms)	162.2 (0.6)	165.7 (0.6)	3.5 (1.8 , 5.2)	2.0 (0.2 , 3.8)
QTc interval (ms)	413.9 (0.5)	416.2 (0.6)	2.3 (0.8 , 3.9)	2.4 (0.9 , 4.0)
P axis (°)	48.3 (0.6)	42.7 (0.6)	-5.6 (-7.3 , -3.9)	-5.3 (-7.2 , -3.5)
T axis (°)	39.0 (0.6)	35.5 (0.7)	-3.5 (-5.3 , -1.7)	-3.1 (-5.0 , -1.1)
QRS axis (°)	38.7 (0.8)	21.1 (0.9)	-17.6 (-19.9 , -15.3)	-14.5 (-16.8 , -12.2)
Small Q-wave (%)	5.3	9.2	3.8 (2.1 , 5.6)	3.0 (1.1 , 4.8)

Data are presented as mean (se) or percentage. Results were based on weighted linear regression analysis.
[1]Multivariate model adjusted for age, sex, ethnicity, smoking, alcohol intake, education level, physical activity and statin use

REFERENCES

1. WHO. Obesity: preventing and managing the global epidemic: report of a WHO consultation. Technical Report Series 894. Geneva: WHO; 2000.
2. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med. 2006;119:812-9.
3. Esteghamati A, Hafezi-Nejad N, Sheikhbahaei S, Heidari B, Zandieh A, Ebadi M, et al. Risk of coronary heart disease associated with metabolic syndrome and its individual components in Iranian subjects: a matched cohort study. J Clin Lipidol. 2014;8:279-86.
4. Vaya A, Martinez-Triguero ML, Espana F, Todoli JA, Bonet E, Corella D. The metabolic syndrome and its individual components: its association with venous thromboembolism in a Mediterranean population. Metab Syndr Relat Disord. 2011;9:197-201.
5. Mehta RH, Westerhout CM, Zheng Y, Giugliano RP, Huber K, Prabhakaran D, et al. Association of metabolic syndrome and its individual components with outcomes among patients with high-risk non-ST-segment elevation acute coronary syndromes. Am Heart J. 2014;168:182-8 e1.
6. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. Diabetes. 1998;47:699-713.
7. Isik T, Tanboga IH, Kurt M, Kaya A, Ekinci M, Ayhan E, et al. Relation of the metabolic syndrome with proarrhythmogenic electrocardiographic parameters in patients without overt diabetes. Acta Cardiol. 2012;67:195-201.
8. Safar ME, Thomas F, Blacher J, Nzietchueng R, Bureau JM, Pannier B, et al. Metabolic syndrome and age-related progression of aortic stiffness. J Am Coll Cardiol. 2006;47:72-5.
9. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013;28:513-23.
10. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56:1163-9.
11. Man SC, Maan AC, van der Wall EE, Schalij MJ, Swenne CA. Beats: an interactive research oriented ECG analysis system. Comput Cardiol. 2010;37:1007-10.
12. Draisma HHM, Swenne CA, van der Vooren H, Maan AC, Hooft van Huysduynen B, van der Wall EE, et al. LEADS: an interactive research oriented ECG/VCG analysis system. Comput Cardiol. 2005;32:515-8.
13. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in population studies. A classification system. Circulation. 1960;21:1160-75.
14. Macfarlane PW, Devine B, Clark E. The University of Glasgow (Uni-G) ECG Analysis Program. Comput Cardiol. 2005:451-4.
15. Macfarlane PW, Devine B, Latif S, McLaughlin S, Shoat DB, Watts MP. Methodology of ECG interpretation in the Glasgow program. Methods Inf Med. 1990;29:354-61.
16. Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, et al. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. Am J Epidemiol. 1999;149:853-62.
17. Dhingra R, Pencina MJ, Wang TJ, Nam BH, Benjamin EJ, Levy D, et al. Electrocardiographic QRS duration and the risk of congestive heart failure: the Framingham Heart Study. Hypertension. 2006;47:861-7.

18. Rabkin SW, Mathewson FA, Tate RB. The relationship of marked left axis deviation to the risk of ischemic heart disease. Int J Cardiol. 1981;1:169-78.
19. Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. Am Heart J. 1998;135:733-8.
20. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735-52.
21. Lumley T. Analysis of complex survey samples. J Stat Softw. 2004; 9:1-19.
22. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health. 1991;81:1166-73.
23. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. The Am J Cardiol. 1993;72:23B-5B.
24. Magnani JW, Johnson VM, Sullivan LM, Gorodeski EZ, Schnabel RB, Lubitz SA, et al. P wave duration and risk of longitudinal atrial fibrillation in persons >/= 60 years old (from the Framingham Heart Study). Am J Cardiol. 2011;107:917-21 e1.
25. Rautaharju PM, Nelson JC, Kronmal RA, Zhang ZM, Robbins J, Gottdiener JS, et al. Usefulness of T-axis deviation as an independent risk indicator for incident cardiac events in older men and women free from coronary heart disease (the Cardiovascular Health Study). Am J Cardiol. 2001;88:118-23.
26. Li Y, Shah AJ, Soliman EZ. Effect of electrocardiographic P-wave axis on mortality. Am J Cardiol. 2014;113:372-6.
27. Higashiyama A, Hozawa A, Murakami Y, Okamura T, Watanabe M, Nakamura Y, et al. Prognostic value of q wave for cardiovascular death in a 19-year prospective study of the Japanese general population. J Atheroscler Thromb. 2009;16:40-50.
28. Ebong IA, Bertoni AG, Soliman EZ, Guo M, Sibley CT, Chen YD, et al. Electrocardiographic abnormalities associated with the metabolic syndrome and its components: the multi-ethnic study of atherosclerosis. Metab Syndr Relat Disord. 2012;10:92-7.
29. Jiang X, Liu X, Wu S, Zhang GQ, Peng M, Wu Y, et al. Metabolic syndrome is associated with and predicted by resting heart rate: a cross-sectional and longitudinal study. Heart. 2015;101:44-9.
30. Rodriguez-Colon SM, He F, Bixler EO, Fernandez-Mendoza J, Vgontzas AN, Calhoun S, et al. Metabolic syndrome burden in apparently healthy adolescents is adversely associated with cardiac autonomic modulation--Penn State Children Cohort. Metab Clin Exp. 2015;64:626-32.
31. Assanelli D, Rago L, Salvetti M, Di Castelnuovo A, Badilini F, Vaglio M, et al. T-wave axis deviation, metabolic syndrome and cardiovascular risk: results from the MOLI-SANI study. J Electrocardiol. 2012;45:546-50.
32. Bacharova L, Krivosikova Z, Wsolova L, Gajdos M. Alterations in the QRS complex in the offspring of patients with metabolic syndrome and diabetes mellitus: early evidence of cardiovascular pathology. J Electrocardiol. 2012;45:244-51.
33. Kim JY, Mun HS, Lee BK, Yoon SB, Choi EY, Min PK, et al. Impact of metabolic syndrome and its individual components on the presence and severity of angiographic coronary artery disease. Yonsei Med J. 2010;51:676-82.
34. Solymoss BC, Bourassa MG, Campeau L, Sniderman A, Marcil M, Lesperance J, et al. Effect of increasing metabolic syndrome score on atherosclerotic risk profile and coronary artery disease angiographic severity. Am J Cardiol. 2004;93:159-64.

35. Voulgari C, Tentolouris N, Dilaveris P, Tousoulis D, Katsilambros N, Stefanadis C. Increased heart failure risk in normal-weight people with metabolic syndrome compared with metabolically healthy obese individuals. J Am Coll Cardiol. 2011;58:1343-50.
36. Eisenstein I, Edelstein J, Sarma R, Sanmarco M, Selvester RH. The electrocardiogram in obesity. J Electrocardiol. 1982;15:115-8.
37. Landsberg L. Diet, obesity and hypertension: an hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. Q J Med. 1986;61:1081-90.
38. Hillebrand S, de Mutsert R, Christen T, Maan AC, Jukema JW, Lamb HJ, et al. Body fat, especially visceral fat, is associated with electrocardiographic measures of sympathetic activation. Obesity. 2014;22:1553-9.
39. Alpert MA, Terry BE, Cohen MV, Fan TM, Painter JA, Massey CV. The electrocardiogram in morbid obesity. The Am J Cardiol. 2000;85:908-10, A10.
40. Sun GZ, Li Y, Zhou XH, Guo XF, Zhang XG, Zheng LQ, et al. Association between obesity and ECG variables in children and adolescents: A cross-sectional study. Exp Ther Med. 2013;6:1455-62.
41. Magnani JW, Lopez FL, Soliman EZ, Maclehose RF, Crow RS, Alonso A. P wave indices, obesity, and the metabolic syndrome: the atherosclerosis risk in communities study. Obesity. 2012;20:666-72.
42. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. Physiological reviews. 2008;88:389-419.
43. Qasim A, Mehta NN, Tadesse MG, Wolfe ML, Rhodes T, Girman C, et al. Adipokines, insulin resistance, and coronary artery calcification. J Am Coll Cardiol. 2008;52:231-6.

CHAPTER 4

Relation of overall and abdominal adiposity with electrocardiogram parameters of subclinical cardiovascular disease in individuals aged 45 to 65 years (from the Netherlands Epidemiology of Obesity study)

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ABSTRACT

Background

Overall and abdominal obesity are well-established risk factors for cardiometabolic disease. However, associations of overall and abdominal adiposity with electrocardiographic (ECG) markers of subclinical cardiovascular disease (CVD) have not yet been fully elucidated. Therefore, we investigated these associations in a population without preexisting CVD.

Methods

We performed cross-sectional analyses in the Netherlands Epidemiology of Obesity Study. Body mass index (BMI), total body fat, and waist circumference were assessed in all participants, and abdominal subcutaneous adipose tissue and visceral adipose tissue (by magnetic resonance imaging) were assessed in a random subgroup. ECG parameters were determined using 12-lead electrocardiograms. We performed linear regression analyses, adjusting for potential confounding factors and, when investigating abdominal adiposity, additionally for total body fat.

Results

After exclusion of participants with preexisting CVD (n = 654), 5939 individuals (42% men) were analyzed, with a mean (SD) age of 55 (6) years and BMI of 26.3 (4.4) kg/m^2. Measures of both overall and abdominal adiposity were associated with ECG parameters but none of these measures was more strongly associated than the others. For example, heart rate (beats/min) increased per SD higher BMI (2.2; 95% confidence interval 1.9, 2.5), total body fat (2.9; 2.4, 3.4), subcutaneous adipose tissue (2.3;1.7, 2.9), waist circumference (2.1; 1.4, 2.8), and visceral adipose tissue (1.7; 0.8, 2.5). In subgroup analyses based on gender and cardiovascular risk factors, no consistent interactions were observed.

Conclusions

In conclusion, in a middle-aged population without preexisting CVD, measures of both overall and abdominal adiposity were associated with ECG parameters. Future studies should evaluate the added value of adiposity measures in electrocardiography-based diagnoses and the prognostic value of adding adiposity measures to risk prediction tools.

INTRODUCTION

Several studies have shown that high abdominal fat, especially excess visceral adipose tissue (VAT), plays an important role in the increased cardiometabolic risk associated with excess fat mass, on top of the important role that overall adiposity plays [1-3]. Both overall and abdominal adiposity have been associated with cardiovascular end points, and more rarely with subclinical cardiovascular disease (CVD) [4-8]. Excess fat mass is often assessed by body mass index (BMI); however, this might not be the best measure because it does not distinguish fat mass from fat-free mass. Total body fat and subcutaneous adipose tissue are more accurate measures of overall adiposity, and waist circumference and VAT are more accurate measures of abdominal adiposity. Reports on associations between both measures of overall and abdominal adiposity and commonly used electrocardiographic (ECG) parameters indicative of subclinical CVD (in a population without preexisting CVD) are scarce. Electrocardiography is widely used in clinical practice for diagnostics and also has significant prognostic value for CVD and mortality [9]. We therefore focused on subtle changes in ECG parameters, which do not have immediate obvious importance, but that have previously been associated with a broad range of future cardiovascular abnormalities or mortality [10-17]. We aimed to investigate associations between measures of overall and abdominal adiposity and ECG parameters in a population without preexisting CVD.

METHODS

The Netherlands Epidemiology of Obesity (NEO) Study is a prospective, population-based cohort study with 6671 individuals, included between 2008 and 2012. Men and women aged between 45 and 65 years, living in the area of greater Leiden (in the Netherlands), and with a BMI ≥ 27 kg/m^2 were eligible to participate. In addition, all inhabitants aged between 45 and 65 years from 1 municipality (Leiderdorp) were invited to join irrespective of their BMI, allowing a reference distribution of BMI. Participants completed a questionnaire on demographic and clinical information before the visit to the NEO study center. Participants were invited to a baseline visit at the NEO study center after an overnight fast. Participants with preexisting CVD were excluded from the present analyses because we were interested in subclinical CVD. Preexisting CVD was defined as either self-reported myocardial infarction, angina, congestive heart failure, stroke or peripheral vascular disease, or as presence of Minnesota codes for atrial fibrillation, left bundle branch block, right bundle branch block or Wolff-Parkinson-White syndrome, or as presence of an artificial pacemaker [18]. Additionally, individuals with missing electrocardiograms were excluded. More information on the study design and population has been published elsewhere [19]. The Medical Ethics Committee of the Leiden University Medical Center approved the design of the study. All participants gave their written informed consent.

Ethnicity was self-reported in 8 categories on the questionnaire and then grouped into white and other. Education level was grouped as low (none, primary school, or lower vocational education) and high education (intermediate secondary education, middle-level vocational education, higher secondary education, higher professional education, university, or other). Tobacco smoking was categorized into current, former, or never smokers. Alcohol

consumption was reported on a food frequency questionnaire and recalculated into gram/day [20]. Participants reported their physical activity using the Short Questionnaire to Assess Health-Enhancing Physical Activity, and physical activity was expressed in hours per week of metabolic equivalents [21]. Participants were asked to bring all medications they were currently using to the study visit. Height and weight were measured without shoes and 1 kg was subtracted from the weight to correct for the weight of clothing. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Waist circumference was measured with a horizontally placed flexible tape in the middle of the distance between the lowest rib and the iliac crest. With a bioimpedance device (TBF-310, Tanita International Division, Yiewsley, United Kingdom), total body fat was estimated. Abdominal subcutaneous adipose tissue and VAT were assessed by magnetic resonance imaging (1.5 T magnetic resonance imaging, Philips Medical Systems, Best, the Netherlands) using a turbo spin echo imaging protocol in a random group of 2580 participants without contraindications for magnetic resonance imaging (most notably metallic devices, claustrophobia, or a body circumference of more than 1.70 m). Three transverse images with a slice thickness of 10 mm were obtained at the level of the fifth lumbar vertebra during a breath-hold. The fat depots were converted from the number of pixels to centimeters squared. In the analyses, the average of the 3 slices was used. Brachial blood pressure was measured in a seated position on the right arm using a validated automatic oscillometric device (OMRON, Model M10-IT, Omron Health Care Inc, Lake Forest, Illinois). Blood pressure was measured 3 times with 5-minute rest between consecutive measurements. The mean systolic and diastolic blood pressure were calculated. Blood was sampled after an overnight fast of 10 hours. Fasting glucose, triglyceride, high-density lipoprotein, and low-density lipoprotein concentrations were measured with the enzymatic colorimetric method (Roche Modular Analytics P800, Roche Diagnostics Mannheim, Germany). A 12-lead electrocardiogram at rest was obtained using a Mortara Eli-350 electrocardiograph (Mortara Instrument Inc., Milwaukee, Wisconsin) after a period of rest of at least 10 minutes. ECGs were stored in a MegaCare electrocardiogram management system (Dräger, Zoetermeer, the Netherlands). Values for heart rate, P-wave duration, QRS complex duration, PR interval, corrected QT interval (corrected according to the Bazett formula), P-wave axis, T-wave axis, and QRS axis were recalculated using the GRI interpretation program, which is part of the management system, to assess subtle changes in ECG parameters, which could indicate subclinical CVD in a population without known overt CVDs [22].

We defined various subgroups to perform stratified analyses in, namely, men or women, high or normal blood pressure levels, serum triglyceride, fasting plasma glucose, serum high-density lipoprotein cholesterol, and serum low-density lipoprotein cholesterol concentrations. Cut-off points were used that were proposed by the National Cholesterol Education Program Adult Treatment Panel III to define the metabolic syndrome, with minor modifications as stated in the American Heart Association and the National Heart, Lung, and Blood Institute statement and additionally also cut-off points for low-density lipoprotein cholesterol [23]. High blood pressure was defined as blood pressure ≥ 130 systolic /≥ 85 mm Hg diastolic or on antihypertensive drug treatment in a patient with a history of hypertension; high serum triglyceride concentrations were defined as serum triglycerides ≥ 150 mg/dl or 1.7 mmol/L or use of prescription drugs to reduce serum triglyceride concentrations; low serum high-density lipoprotein cholesterol was defined as serum high-density lipoprotein

cholesterol < 40 mg/dl or 1.03 mmol/L for men and <50 mg/dl or 1.3 mmol/L for women or use of prescription drugs to elevate serum high-density lipoprotein cholesterol; high fasting plasma glucose was defined as fasting plasma glucose ≥ 100 mg/dl or 5.56 mmol/L or use of prescription drugs to lower plasma glucose concentrations; and high serum low-density lipoprotein cholesterol is defined as serum low-density lipoprotein cholesterol > 160 mg/dl or 4.1 mmol/L or use of prescription drugs to reduce serum low-density lipoprotein cholesterol concentrations.

In the NEO study, there is an oversampling of individuals with a BMI of 27 kg/m^2 or higher. Adjustments for the oversampling of individuals with BMI ≥ 27 kg/m^2 were made to correctly represent baseline associations in the general population. This was done by weighing individuals toward the BMI distribution of participants from the Leiderdorp municipality, whose BMI distribution was similar to the BMI distribution of the general Dutch population [24]. All results are based on weighted analyses. Consequently, the results apply to a population-based study without oversampling of individuals with a BMI ≥ 27 kg/m^2. The data of the baseline characteristics were presented as mean (SD), median (interquartile range), or as percentage. We calculated Z-scores and standardized the adiposity measures to a mean of 0 and a standard deviation of 1. The associations between the measures of overall adiposity (BMI, total body fat, and subcutaneous adipose tissue) and the measures of abdominal adiposity (waist circumference and VAT) with the ECG parameters heart rate (beats/min), P-wave duration (milliseconds), QRS complex duration (milliseconds), PR interval (milliseconds), corrected QT interval (milliseconds), P-wave axis (°), T-wave axis (°), and QRS axis (°) were investigated using linear regression analyses and expressed as difference in ECG parameter with 95% confidence interval (CI). In crude models, the associations of waist circumference and VAT were adjusted for total body fat. Adjusted models were additionally adjusted for age, gender, ethnicity, smoking, alcohol intake, education level, physical activity, presence of chronic obstructive pulmonary disease, and use of several drugs that could influence the ECG parameters, namely, use of digoxin, class I/III blocking medication, β blockers, calcium channel blockers, and QT-prolonging drugs.

Analyses were repeated in the previously described subgroups. We tested for interaction between adiposity measures and subgroups by including product terms in the models. Data were analyzed using STATA version 14 (Statacorp, College Station, Texas, USA).

RESULTS

In the NEO study, 6671 participants were included. For the present analysis, we consecutively excluded participants with a self-reported history of CVD (n = 464), right bundle branch block (n = 95), left bundle branch block (n = 41), atrial fibrillation (n = 42), artificial pacemaker (n = 8), Wolff-Parkinson-White syndrome (n = 4), or missing electrocardiogram (n = 78), leaving 5939 participants for the main analysis. Measurements of visceral and subcutaneous adipose tissue were available in 2331 participants. The baseline characteristics of the study population are presented in Table 1. The mean (SD) age was 55 (6) years and 42% were men. Although women had more total body fat and more subcutaneous adipose tissue, men had higher BMI and more VAT.

Table 1. Characteristics of 5939 participants aged 45 to 65 year from the Netherlands Epidemiology of Obesity study

	Total population	Men (42%)	Women (58%)
Age (years)	55 ± 6	56 ± 6	55 ± 6
Ethnicity, white	95%	95%	95%
Education level, low*	19%	18%	20%
Smoker			
Never	39	36	42
Former	45	46	44
Current	16	18	14
Alcohol intake (grams/day)	9.8 (2.8 , 21.3)	16.4 (6.0 , 28.1)	7.7 (1.6 , 14.8)
Physical activity (MET-hour/week)	29.8 (15.3 , 49.3)	30.7 (15.0 , 50.0)	29.0 (15.8 , 48.5)
Fasting glucose (mmol/l; mg/dl)	5.4 ± 1.0; 98.1 ± 17.1	5.7 ± 1.1; 101.8 ± 20.0	5.3 ± 0.8; 95.4 ± 14.0
Use of glucose lowering therapy	2%	3%	2%
Systolic blood pressure (mmHg)	130.0 ± 17.1	134.4 ± 15.5	126.8 ± 17.5
Diastolic blood pressure (mmHg)	83.2 ± 10.3	85.0 ± 10.1	81.9 ± 10.3
Use of antihypertensive therapy	21%	20%	21%
Triglycerides (mmol/l; mg/dl)	1.0 (0.7 , 1.5); 88.6 (63.8 , 129.3)	1.2 (0.8 , 1.7); 102.7 (72.6 , 148.8)	0.9 (0.7 , 1.3); 81.5 (60.2 ,115.1)
HDL-cholesterol (mmol/l; mg/dl)	1.6 ± 0.5; 61.3 ± 17.8	1.4 ± 0.4; 52.2 ± 14.1	1.8 ± 0.4; 67.9 ± 17.0
LDL-cholesterol (mmol/l; mg/dl)	3.6 ± 1.0; 138.2 ± 37.2	3.6 ± 1.0; 138.8 ± 38.1	3.6 ± 0.9; 137.8 ± 36.5
Use of lipid lowering therapy	8%	11%	6%
Waist circumference (cm)	91.8 ± 13.2	98.0 ± 11.3	87.2 ± 12.5
BMI (kg/m^2)	26.3 ± 4.4	26.8 ± 3.8	25.9 ± 4.7
Total body fat (%)	31.8 ± 8.7	24.8 ± 6.0	36.9 ± 6.4
VAT (cm^2) (n=2331)	88.3 ± 55.2	113.5 ± 60.4	66.4 ± 40.3
SAT (cm^2) (n=2331)	234.6 ± 96.5	207.1 ± 84.2	258.4 ± 98.3

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MET, metabolic equivalent of task; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.
Results were based on analyses weighted towards the BMI distribution of the general population (n=5939).
Results are presented as mean ± SD, median (IQR) or percentage.
* lower education: none, primary school, lower vocational education

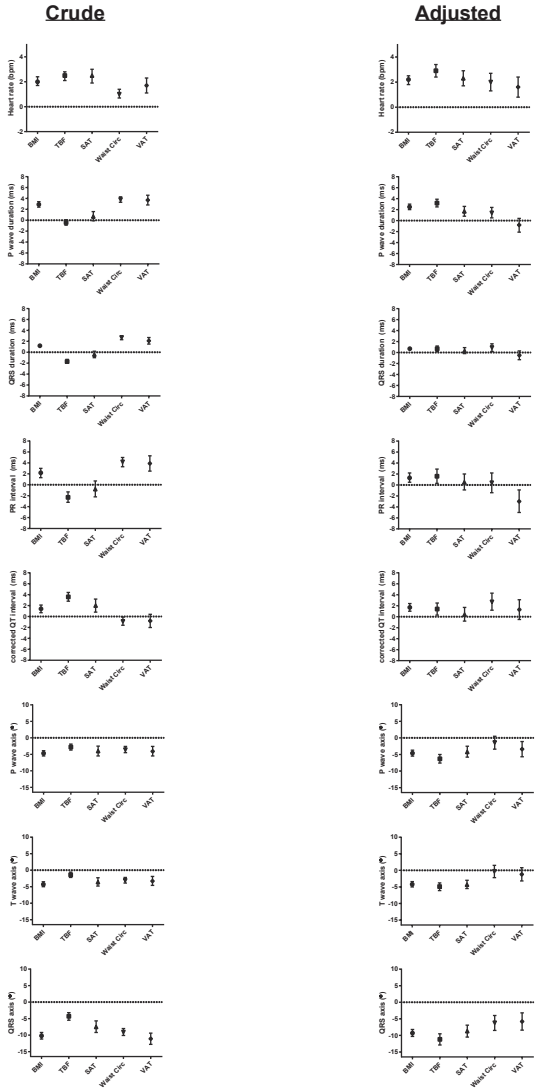

Figure 1. Associations of standardized obesity measures with electrocardiographic (ECG) parameters in 5939 participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity Study (2331 with VAT and SAT). Results were based on linear regression analyses weighed toward the BMI distribution of the general population (n = 5939), and expressed as difference in the ECG parameter (with 95% confidence interval) per standard deviation of adiposity measure. Crude: Associations with waist circumference or VAT are adjusted for TBF. Adjusted: Adjusted for age, gender, ethnicity, smoking, alcohol intake, education level, physical activity, presence of chronic obstructive pulmonary disease, and use of digoxin, class I/III blocking medication, β blockers, calcium channel blockers, and QT-prolonging drugs. Associations with waist circumference or VAT are additionally adjusted for TBF. Standard deviations: BMI 4.4 kg/m^2 ; TBF 8.7%; SAT 96.6 cm^2 ; Waist circ 13.2 cm; VAT 55.2 cm^2 . BMI = body mass index; SAT = subcutaneous adipose tissue; TBF = total body fat; VAT = visceral adipose tissue; Waist Circ = waist circumference.

Figure 1 is a graphical representation of the associations of the standardized measures of overall and abdominal adiposity with all ECG parameters. The crude model shows associations of all adiposity measures with heart rate, P-wave axis, T-wave axis, and QRS axis, and less consistent associations for P-wave duration, QRS duration, PR interval, and corrected QT interval. The adjusted model showed that both measures of abdominal and overall adiposity were associated with higher heart rate. For example, 1 SD higher total body fat was associated with 2.9 beats/min higher heart rate (95% CI 2.4, 3.4) and 1 SD higher VAT with 1.7 beats/min (0.8, 2.5) higher heart rate. All measures of adiposity were associated with P-wave duration except for VAT adjusted for total body fat (β −0.8 millisecond; 95% CI −2.1, 0.4). BMI, total body fat, and waist circumference were positively associated with QRS duration, whereas no associations were found for subcutaneous adipose tissue (0.4 millisecond; −0.2, 1.0) and VAT (−0.5 millisecond; −1.3, 0.4). BMI (1.3 milliseconds; 0.4, 2.1) and total body fat (1.5 milliseconds; 0.2, 2.8) were positively associated with PR interval, whereas no associations were found for subcutaneous adipose tissue and waist circumference, and the association of VAT was, if anything, in the opposite direction (−2.9 milliseconds; −5.0, −0.9). All measures of adiposity were associated with longer corrected QT interval, except for subcutaneous adipose tissue (0.6 millisecond; −0.7, 1.9). All measures of overall adiposity were associated with P-wave axis, T-wave axis, and QRS axis. Furthermore, waist circumference was negatively associated with QRS axis (−6.2°; −8.4, −4.0), but not with P-wave axis (−1.3°; −3.3, 0.6) or T-wave axis (−0.3°; −2.1, 1.5). VAT was negatively associated with P-wave axis (−3.4°; −5.7, −1.1) and QRS axis (−6.0°; −8.5, −3.4), but not with T-wave axis (−1.3°; −3.3, 0.7). Including participants with preexisting CVD in the analyses did not materially change the results.

In Figure 2, associations between measures of overall and abdominal adiposity with ECG parameters are shown in men and women in adjusted models. In summary, no major or consistent differences were found between men and women in the association between overall and abdominal adiposity and any of the ECG parameters. Measures of both overall and abdominal adiposity were associated with a higher heart rate in both men and women. In both men and women, BMI, total body fat, subcutaneous adipose tissue, and waist circumference were associated with a longer P-wave duration, but VAT adjusted for total body fat was not associated with P-wave duration (per SD VAT in men: β −0.6 millisecond; 95%CI: −2.2, 1.1 and in women: −0.6 millisecond; −2.4, 1.3). Measures of both overall and abdominal adiposity showed associations with a longer QRS duration in men, except for VAT (−0.3 millisecond; −1.2, 0.5). In women, only BMI (0.5 millisecond; 0.1, 1.0) was associated with longer QRS duration. For PR interval, only in women associations were found with BMI and total body fat. Associations of total body fat were stronger in women than in men. In women, 1 SD higher TBF was associated with a 2.9 millisecond (95% CI 1.3, 4.5) longer PR interval, whereas in men, this was −0.9 millisecond (−3.0, 1.2; p-value interaction 0.002). All measures of adiposity showed an association with longer corrected QT interval in both men and women, except for subcutaneous adipose tissue in women (−0.2 millisecond; −1.8, 1.4) and a weak association of VAT in men (1.0 millisecond; −1.2, 3.1). Furthermore, the association of BMI was somewhat stronger in men (3.3 milliseconds; 2.0, 4.6) than in women (1.1 milliseconds; 0.2, 1.9; p-value interaction 0.007). In both men and women, measures of overall and abdominal adiposity were associated with a more leftward shifted P-wave axis, T-wave axis, and QRS axis. Only waist circumference was not associated with P-wave axis in

men (0.5°; −2.65, 3.6), and waist circumference (2.3°; −0.7, 5.2) and VAT (−0.3°; −2.6, 2.1) were not associated with T-wave axis in men.

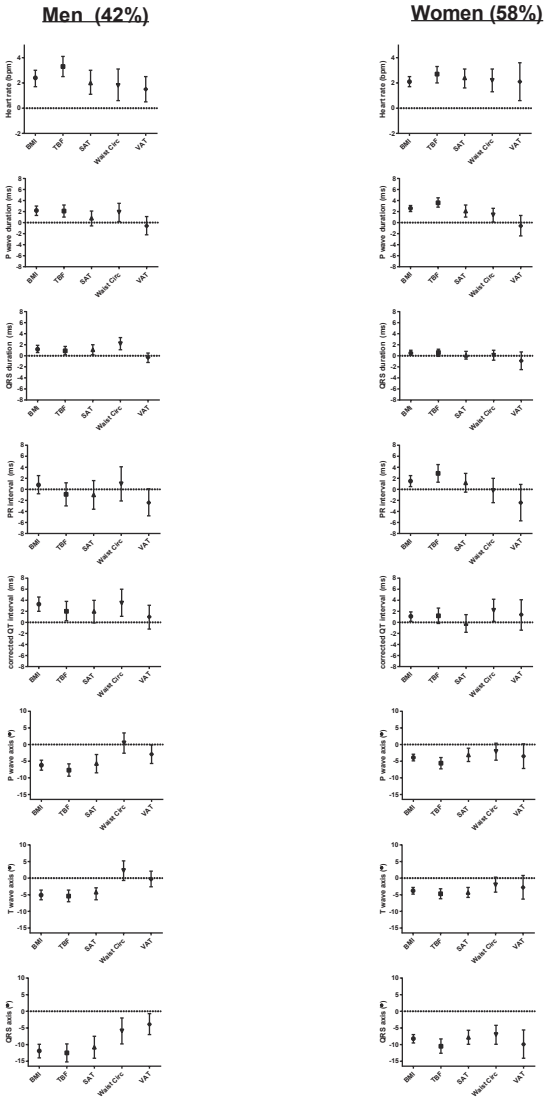

Figure 2. Associations of standardized obesity measures with electrocardiographic (ECG) parameters in men and women aged 45 to 65 years from the Netherlands Epidemiology of Obesity Study (2331 with VAT and SAT). Results were based on linear regression analyses weighed toward the BMI distribution of the general population (n = 5939), and expressed as difference in the ECG parameter (with 95% confidence interval) per standard deviation of adiposity measure. Shown results were adjusted for age, gender, ethnicity, smoking, alcohol intake, education level, physical activity, presence of chronic obstructive pulmonary disease, and use of digoxin, class I/III blocking medication, β blockers, calcium channel blockers, and QT-prolonging drugs. Associations with waist circumference or VAT are

additionally adjusted for TBF. Standard deviations: BMI 4.4 kg/m^2 ; TBF 8.7%; SAT 96.6 cm^2 ; Waist circ 13.2 cm; VAT 55.2 cm^2 . BMI = body mass index; SAT = subcutaneous adipose tissue; TBF = total body fat; VAT = visceral adipose tissue; Waist Circ = waist circumference.

As shown in Supplementary Figure 1, for the other subgroups, results were similar. We observed differences in strengths of association of some measures of overall and abdominal adiposity with ECG parameters between subgroups. However, these differences were inconsistent.

DISCUSSION

In a large cohort of individuals without overt CVD, we investigated the associations between measures of overall adiposity, BMI, total body fat, and subcutaneous adipose tissue, as well as measures of abdominal adiposity, waist circumference, and VAT, with changes in ECG parameters, indicative of subclinical CVD. We observed that measures of both overall and abdominal adiposity were associated with ECG measures associated with subclinical CVD, and that measures of abdominal adiposity were not more strongly associated with ECG measures than measures of overall adiposity. When investigating the associations of adiposity measures with ECG parameters in different subgroups, there were several interactions observed, which were neither consistent with the ECG parameters nor with the specific subgroups. Therefore, we are not able to draw any firm conclusions from these subgroup analyses.

Measures of overall and abdominal adiposity have been associated with subclinical CVD in previous literature. We expected abdominal adiposity to be most strongly associated with ECG parameters since especially VAT is known to release several cytokines, chemokines, and hormones, which can influence organ function and lead to increased progression of atherosclerosis. [1-3]

In this study, measures of abdominal adiposity were not more strongly associated with the ECG parameters than measures of overall adiposity, which could have several explanations. First, it is important to realize that associations with VAT are adjusted for total body fat to look specifically at the VAT and not general adiposity. In this study, associations of VAT were attenuated by this adjustment. Furthermore, it is important to realize which specific subclinical cardiovascular abnormalities are reflected by the different ECG parameters. Higher heart rate reflects, among others, increased sympathetic activity, which has been associated with CVD and events [10,25]. P-wave duration reflects atrial depolarization and is associated with atrial fibrillation [11]. QRS duration reflects ventricular depolarization and prolongation is associated with, among others, congestive heart failure, increased left ventricular mass, and higher cardiovascular mortality [12,26]. PR interval reflects atrial conduction, AV nodal conduction, and conduction in the heart tissue. Inconsistent associations have been reported with atrial fibrillation and cardiovascular mortality [13,27]. QT interval reflects ventricular depolarization and repolarization, and prolongation has been associated with ventricular arrhythmias and adverse prognosis [14]. P-wave axis reflects atrial orientation and conduction and has been associated with increased (cardiovascular) mortality risk [15]. Abnormalities in T-wave axis

reflect ventricular repolarization abnormalities, which have been associated with increased risk of coronary heart disease and heart failure [16]. Abnormalities of the QRS axis, or electrical heart axis, which reflects depolarization in the heart, can have several causes. Literature regarding the prognostic value of an abnormal QRS axis is inconclusive, and associations with increased cardiovascular risk are rarely observed in individuals without cardiac disease [17,28]. The deleterious effects of VAT might be stronger for cardiac abnormalities with large metabolic influences, such as atherosclerosis and less on these ECG parameters that have more to do with cardiac activation or conduction. For example, whereas for subclinical atherosclerosis, abdominal adiposity is often described as the most important, for atrial fibrillation, similar association of waist circumference, waist:hip ratio, and BMI was shown [29]. Furthermore, epicardial adipose tissue, a specific visceral fat depot, might show stronger associations with the ECG parameters investigated in this study because of its anatomic proximity to the myocardium and conduction system [30].

A strength of our study is the large study population (n = 5939 after exclusion of participants with preexisting CVD), which made it possible to easily assess associations with sufficient statistical power. Furthermore, the NEO study has performed deep phenotyping of the participants, which made control of potential confounding factors possible. A limitation of our study is its cross-sectional design, which precludes any causal conclusions. Furthermore, adiposity measures were only investigated at 1 moment in time, not taking into account changes in the different adiposity measures in relation to the development of subclinical CVD. Moreover, self-reported variables used in this study could have been subject to information (recall) bias.

In conclusion, in a population aged 45 to 65 years without preexisting CVD, measures of both overall and abdominal adiposity were positively associated with subtle differences in ECG parameters, associated with subclinical CVD.

Adiposity measures have been proposed to aid in distinguishing people at low and high cardiovascular risk, and this study adds evidence in favor of this potential role of both measures of overall adiposity, as well as abdominal adiposity in risk stratification. The role of abdominal and overall adiposity might differ between abnormalities with large metabolic influences and activation or conduction abnormalities. Moreover, more easily determinable measures, such as BMI or waist circumference, may have greater potential for application in clinical practice than for example VAT. Future studies should evaluate the value of the inclusion of adiposity measures in ECG diagnoses, such as atrial fibrillation or left ventricular hypertrophy, and the prognostic value of adding adiposity measures to current risk prediction tools.

Acknowledgments

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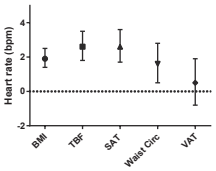
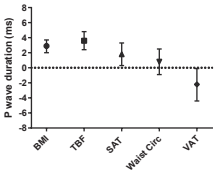
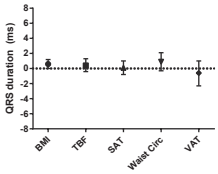
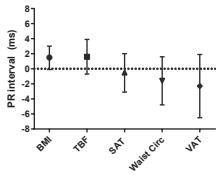
Supplementary Figure 1. Associations of standardized obesity measures with ECG parameters in subgroups of participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity Study (2331 with VAT and SAT). Results were based on linear regression analyses weighed toward the BMI distribution of the general population (n = 5939), and expressed as difference in the ECG parameter (with 95% confidence interval) per standard deviation of adiposity measure. Results were based on weighted linear regression analyses adjusted for age, gender, ethnicity, smoking, alcohol intake, education level, physical activity, presence of chronic obstructive pulmonary disease, and use of digoxin, class I/III blocking medication, β blockers, calcium channel blockers, and QT-prolonging drugs. Associations with waist circumference or VAT are additionally adjusted for TBF. Standard deviations: BMI 4.4 kg/m^2; TBF 8.7%; SAT 96.6 cm^2; Waist circ 13.2 cm; VAT 55.2 cm^2. High blood pressure: ≥130 systolic/≥85 mm Hg diastolic or on antihypertensive drug treatment in a patient with a history of hypertension; high triglyceride concentration: ≥150 mg/dl or 1.7 mmol/L or use of prescription drugs to reduce serum triglyceride concentrations; high glucose concentration: ≥100 mg/dl or 5.56 mmol/L or use of prescription drugs to lower plasma glucose concentrations; high low-density lipoprotein cholesterol concentration: >160 mg/dl or 4.1 mmol/L or use of prescription drugs to reduce serum low-density lipoprotein cholesterol concentrations; low high-density lipoprotein cholesterol concentrations: <40 mg/dl or 1.03 mmol/L for men and <50 mg/dl or 1.3 mmol/L for women or use of prescription drugs to elevate serum high-density lipoprotein cholesterol. BMI = body mass index; SAT = subcutaneous adipose tissue; TBF = total body fat; VAT = visceral adipose tissue; Waist Circ = waist circumference.

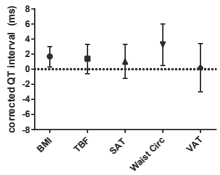
Normal blood pressure (40%)

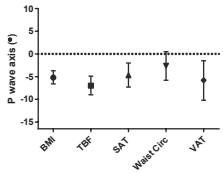


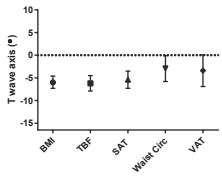


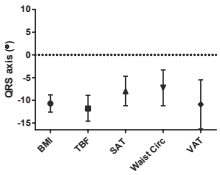




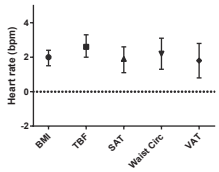


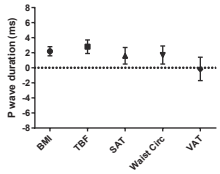


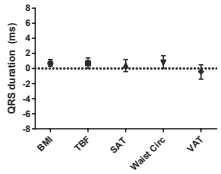


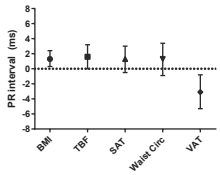


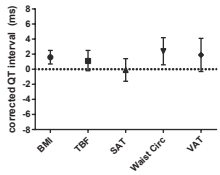
↑ blood pressure (60%)

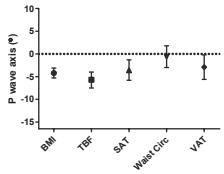


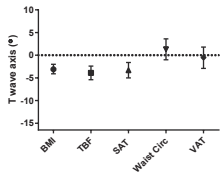


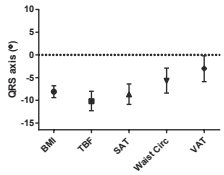




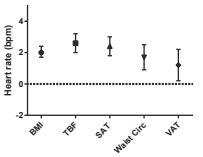


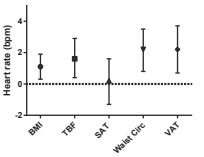


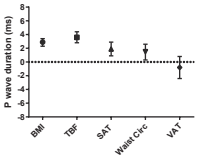


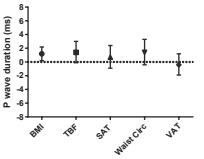


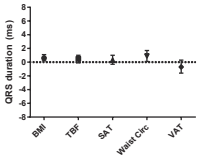
Normal triglyceride concentration (83%) **↑ triglyceride concentration (17%)**

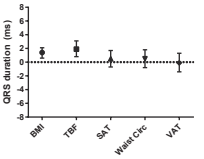


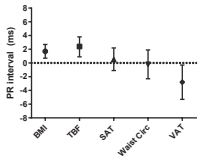


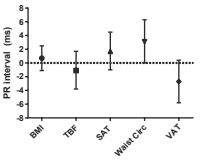


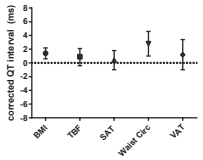


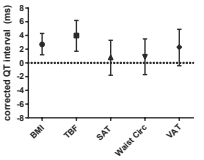


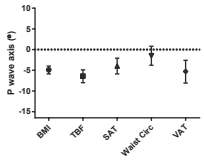


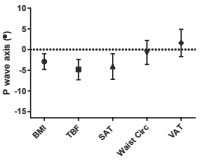


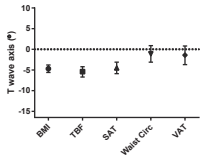


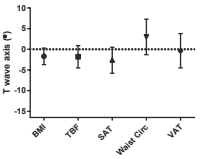


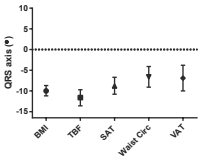


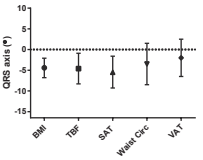




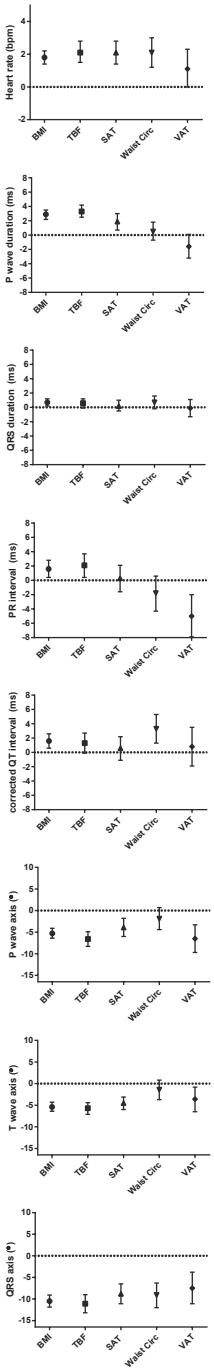




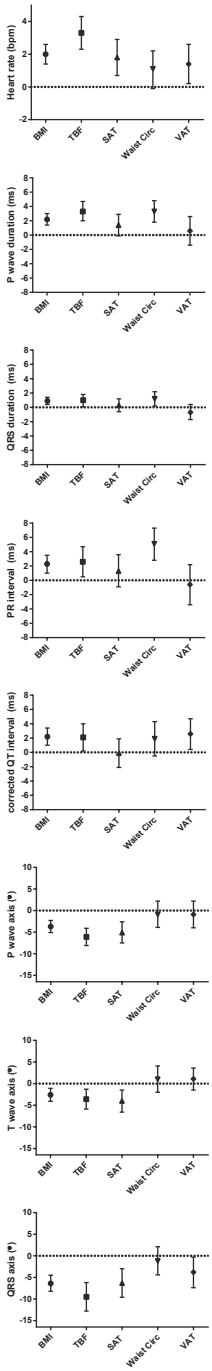




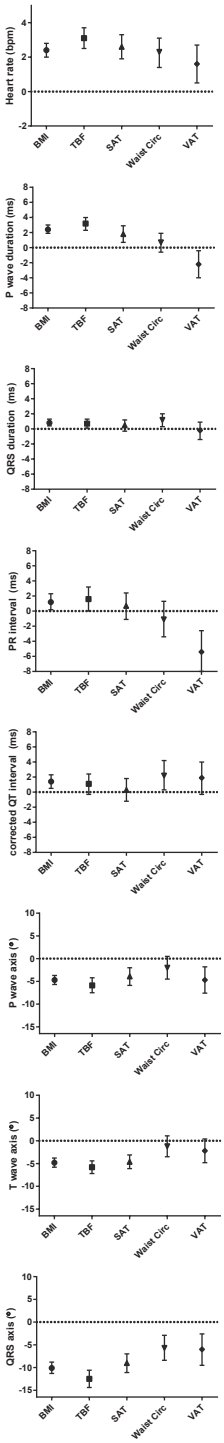
Normal glucose concentration (70%)



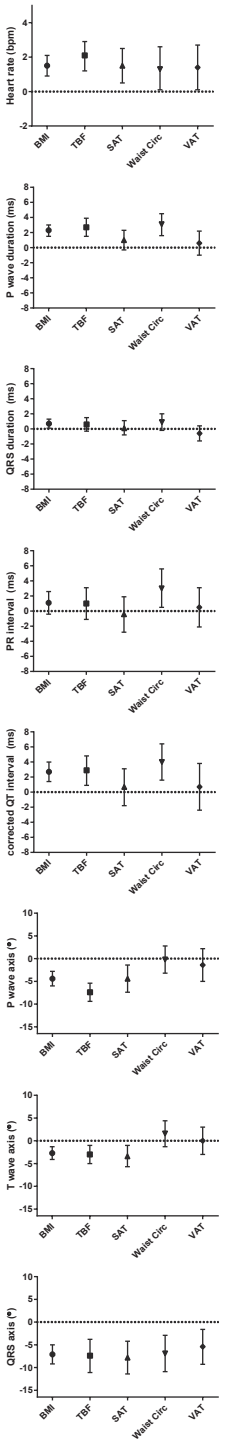
↑ glucose concentration (30%)



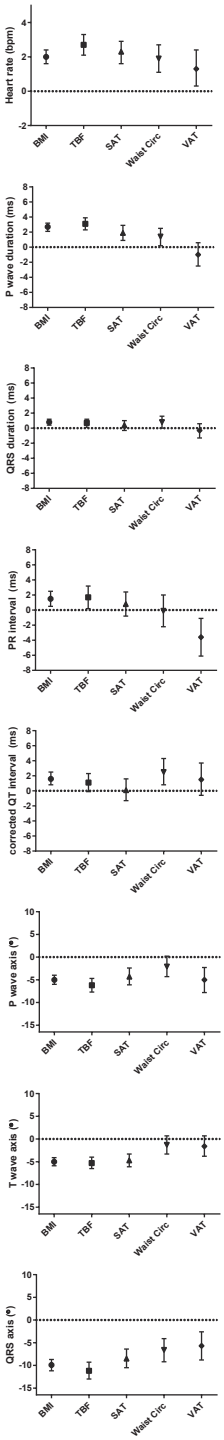
Normal LDL concentration (66%)



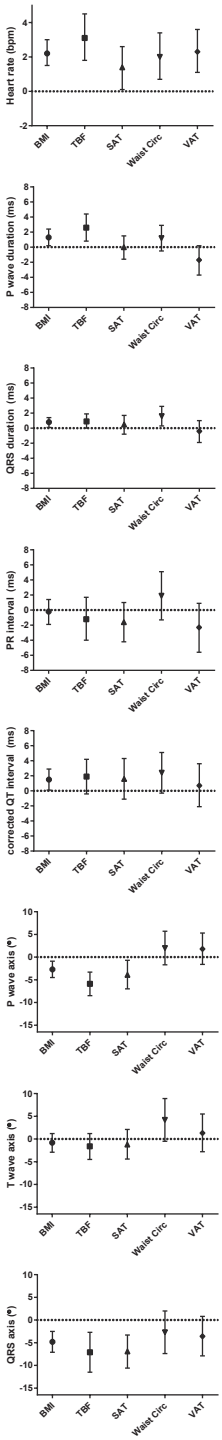
↑ LDL concentration (34%)



Normal HDL concentration (84%)



↓ HDL concentration (16%)



REFERENCES

1. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444:881-7.
2. Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005;96:939-49.
3. de Heredia FP, Gomez-Martinez S, Marcos A. Obesity, inflammation and the immune system. Proc Nutr Soc. 2012;71:332-8.
4. Rexrode KM, Buring JE, Manson JE. Abdominal and total adiposity and risk of coronary heart disease in men. Int J Obes Relat Metab Disord. 2001;25:1047-56.
5. Gast KB, den Heijer M, Smit JW, Widya RL, Lamb HJ, de Roos A, et al. Individual contributions of visceral fat and total body fat to subclinical atherosclerosis: The NEO study. Atherosclerosis. 2015;241:547-54.
6. Lear SA, Humphries KH, Kohli S, Frohlich JJ, Birmingham CL, Mancini GB. Visceral adipose tissue, a potential risk factor for carotid atherosclerosis: results of the Multicultural Community Health Assessment Trial (M-CHAT). Stroke. 2007;38:2422-9.
7. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med. 2008;359:2105-20.
8. Takami R, Takeda N, Hayashi M, Sasaki A, Kawachi S, Yoshino K, et al. Body fatness and fat distribution as predictors of metabolic abnormalities and early carotid atherosclerosis. Diabetes care. 2001;24:1248-52.
9. De Bacquer D, De Backer G, Kornitzer M, Blackburn H. Prognostic value of ECG findings for total, cardiovascular disease, and coronary heart disease death in men and women. Heart. 1998;80:570-7.
10. Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, et al. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. Am J Epidemiol. 1999;149:853-62.
11. Magnani JW, Johnson VM, Sullivan LM, Gorodeski EZ, Schnabel RB, Lubitz SA, et al. P wave duration and risk of longitudinal atrial fibrillation in persons >/= 60 years old (from the Framingham Heart Study). Am J Cardiol. 2011;107:917-21 e1.
12. Kurl S, Makikallio TH, Rautaharju P, Kiviniemi V, Laukkanen JA. Duration of QRS complex in resting electrocardiogram is a predictor of sudden cardiac death in men. Circulation. 2012;125:2588-94.
13. Nielsen JB, Pietersen A, Graff C, Lind B, Struijk JJ, Olesen MS, et al. Risk of atrial fibrillation as a function of the electrocardiographic PR interval: results from the Copenhagen ECG Study. Heart rhythm. 2013;10:1249-56.
14. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardiol. 1993;72:23B-5B.
15. Li Y, Shah AJ, Soliman EZ. Effect of electrocardiographic P-wave axis on mortality. Am J Cardiol. 2014;113:372-6.
16. Rautaharju PM, Nelson JC, Kronmal RA, Zhang ZM, Robbins J, Gottdiener JS, et al. Usefulness of T-axis deviation as an independent risk indicator for incident cardiac events in older men and women free from coronary heart disease (the Cardiovascular Health Study). Am J Cardiol. 2001;88:118-23.
17. Rabkin SW, Mathewson FA, Tate RB. The relationship of marked left axis deviation to the risk of ischemic heart disease. Int J Cardiol. 1981;1:169-78.

18. Prineas RJ CR, Blackburn HW. The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification. Boston, MA: John Wright; 1982.
19. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013;28:513-23.
20. Verkleij-Hagoort AC, de Vries JH, Stegers MP, Lindemans J, Ursem NT, Steegers-Theunissen RP. Validation of the assessment of folate and vitamin B12 intake in women of reproductive age: the method of triads. Eur J Clin Nutr. 2007;61:610-5.
21. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. Journal of clinical epidemiology. 2003;56:1163-9.
22. Macfarlane PW, Devine B, Clark E. The University of Glasgow (Uni-G) ECG Analysis Program. Comput Cardiol. 2005:451-4.
23. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735-52.
24. Ministerie van VWS. Hoeveel mensen hebben overgewicht? NdMG. 2014.
25. Manfrini O, Pizzi C, Viecca M, Bugiardini R. Abnormalities of cardiac autonomic nervous activity correlate with expansive coronary artery remodeling. Atherosclerosis. 2008;197:183-9.
26. Dhingra R, Pencina MJ, Wang TJ, Nam BH, Benjamin EJ, Levy D, et al. Electrocardiographic QRS duration and the risk of congestive heart failure: the Framingham Heart Study. Hypertension. 2006;47:861-7.
27. Aro AL, Anttonen O, Kerola T, Junttila MJ, Tikkanen JT, Rissanen HA, et al. Prognostic significance of prolonged PR interval in the general population. Eur H j. 2014;35:123-9.
28. Aro AL, Huikuri HV, Tikkanen JT, Junttila MJ, Rissanen HA, Reunanen A, et al. QRS-T angle as a predictor of sudden cardiac death in a middle-aged general population. Europace. 2012;14:872-6.
29. Wong CX, Sun MT, Odutayo A, Emdin CA, Mahajan R, Lau DH, et al. Associations of Epicardial, Abdominal, and Overall Adiposity With Atrial Fibrillation. Circ Arrhythm Electrophysiol. 2016;9.
30. Friedman DJ, Wang N, Meigs JB, Hoffmann U, Massaro JM, Fox CS, et al. Pericardial fat is associated with atrial conduction: the Framingham Heart Study. J Am Heart Assoc. 2014;3:e000477.

CHAPTER 5

Borderline Q-waves in individuals without overt cardiovascular disease: relations with adiposity, subclinical atherosclerosis and vascular stiffness

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ABSTRACT

Background

Characteristics and risk factors associated with electrocardiographic borderline Q-waves are not fully elucidated, especially in individuals without overt cardiovascular disease (CVD). Also, the relation of isolated and non-isolated borderline Q-waves with subclinical atherosclerosis and vascular stiffness is unknown.

Methods

We included 5746 Netherlands Epidemiology of Obesity study participants without overt CVD. Participants were divided in three groups: no Q-waves (93.7%), isolated (4.6%) and non-isolated borderline Q-waves (1.7%). Borderline Q-waves were defined as Minnesota Codes 1.2.x and 1.3.x and non-isolated as ≥1 of abnormal QRS axis, left ventricular hypertrophy or ST/T abnormalities. Several characteristics and measures of body fat were assessed. Vascular stiffness was assessed by pulse wave velocity (PWV) and subclinical atherosclerosis by carotid intima-media thickness (cIMT).

Results

Percentage of men, alcohol intake, blood pressure and fasting glucose concentrations were, compared with no Q-waves, higher in the isolated and highest in the non-isolated borderline Q-wave group. Isolated borderline Q-waves were associated with higher body mass index (difference compared with no Q-waves: 1.0 kg/m^2 ; 95%CI: 0.3–1.7; p-value: 0.006), waist circumference (3.4 cm; 1.0–5.8; 0.005), and visceral adipose tissue (21.9 cm^2 ; 7.4–36.3; 0.003) and differences were even larger for nonisolated borderline Q-waves. Compared with no Q-waves, non-isolated borderline Q-waves were associated with higher PWV (1.2 m/s; 0.4–2.0; 0.004) and cIMT (23.4 μm; 3.0–43.8; 0.024), whereas isolated borderline Q-waves were not.

Conclusions

Cardiovascular risk factors and measures of body fat, especially abdominal adiposity, were higher in participants with isolated borderline Q-waves, compared with no Q-waves, and highest in the non-isolated borderline Q-wave group. Non-isolated borderline Q-waves were associated with subclinical atherosclerosis and vascular stiffness. Future studies should investigate potential added value of borderline Q-waves in CVD prediction.

INTRODUCTION

The electrocardiogram (ECG) is commonly used in medical practice to assess the electrical activity in the heart, and abnormalities seen on an individual's ECG can have clinically relevant prognostic or diagnostic value for cardiovascular diseases (CVD)[1,2]. Large Q-waves on an ECG can be seen after a myocardial infarction, but can also be seen in apparently 'healthy' individuals, in whom they are thought to reflect silent ischemia [3]. Next to large Q-waves, smaller abnormalities, such as borderline Q-waves can also be found on the ECG of an individual with or without established cardiovascular disease (CVD), and may be associated with subclinical cardiovascular pathology. Without other ECG abnormalities present, these borderline Q-waves are considered isolated. However they can also be non-isolated, i.e. co-existing with other ECG abnormalities. Clinical characteristics and risk factor profiles of individuals with these borderline Q-waves are not fully elucidated, especially not in individuals without known CVD. In large cohort studies, it was observed that individuals with borderline Q-waves tended to be older, more often suffering from diabetes mellitus and hypertension and also seemed to have a worse kidney function than individuals without Q-waves [4-6]. Although these characteristics suggest an unfavourable metabolic profile, associations with body mass index (BMI) were not demonstrated [4,6]. Although previous studies did not observe an association between BMI and borderline Q-waves, other measures of body fat distribution, notably metabolically active visceral fat, might be associated with borderline Q-waves [7]. It is well-established that in particular abdominal adiposity is associated with CVD and mortality [7-9]. This association with abdominal adiposity could also be present for borderline Q-waves.

Furthermore, the clinical relevance of a borderline Q-wave, especially an isolated borderline Q-wave, in an individual without previously known CVD is not clear. The literature is inconclusive on the importance of borderline, and especially isolated borderline Q-waves in individuals free of established CVD, with some studies reporting increased cardiovascular risk in individuals with borderline Q-waves [4], some reporting no increased cardiovascular risk [5] and some studies reporting increased cardiovascular risk for non-isolated borderline Q-waves only [6].

Consequently, the present study was conducted with two aims. Firstly, we aimed to investigate clinical characteristics and measures of body fat distribution in individuals without Q-waves, with isolated borderline Q-waves and with non-isolated borderline Q-waves. Secondly, we aimed to investigate measures of subclinical atherosclerosis and vascular stiffness in individuals with isolated and non-isolated borderline Q-waves compared with individuals without Q-waves.

METHODS

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based, prospective cohort study designed to investigate pathways that lead to obesity-related diseases, in which 6671 individuals were enrolled between 2008 and 2012. Men and women aged between 45

and 65 years with a self-reported BMI of 27 kg/m^2 or higher living in the area of greater Leiden (in 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 to join irrespective of their BMI, allowing for a reference distribution of BMI. Individuals were invited to a baseline visit at the NEO study centre of the Leiden University Medical Center after an overnight fast. At the time of inclusion, individuals completed a screening form, which enquired about anything that might create a health risk or that might interfere with imaging (most notably metallic devices, claustrophobia, or a body circumference of more than 1.70 m). Of the participants without contra-indications for MRI, approximately 35% were randomly selected to undergo MRI. Prior to the study visit, participants completed a questionnaire at home with demographic, lifestyle, and clinical information. At the study centre all participants underwent an extensive physical examination, including anthropometry, blood sampling, and an ECG. The present analysis is a cross-sectional analysis using the baseline measurements of the NEO study. Participants using QT-prolonging drugs, participants with a history of myocardial infarction or angina pectoris and participants with an artificial pacemaker were excluded from the study population. Furthermore, participants with large Q-waves were excluded from the present study, because we were particularly interested in the clinical relevance of borderline Q-waves. Further details of the study design and population have been described in detail elsewhere [10]. The Medical Ethics Committee of the Leiden University Medical Center approved the design of the study and all participants gave their written informed consent.

Data collection

The ethnicity of participants was self-identified in eight categories on the questionnaire and then grouped into white (>95%) and other. Level of education was reported in 10 categories according to the Dutch education system and grouped as low or high education. Tobacco smoking was categorized into current smoker, former smoker, or never smoker. Alcohol consumption was reported using a food frequency questionnaire and calculated into grams/day [11]. Participants reported the frequency and duration of their physical activity in leisure time which was expressed in hours per week of metabolic equivalents (MET-h/week) using the Short Questionnaire to Assess Health-enhancing physical activity [12]. Participants were asked to bring all the medication they were currently using to the study visit. Brachial blood pressure was measured in a seated position on the right arm using a validated automatic oscillometric device (OMRON, Model M10-IT, Omron Health Care Inc, IL, USA). Blood pressure was measured three times with 5 minutes rest between consecutive measurements. The mean systolic and diastolic blood pressure were calculated. Blood samples were drawn after an overnight fast of 10 hours. Fasting glucose, triglyceride and high-density lipoprotein concentrations as well as creatinine concentration were measured with standard methods in the central clinical chemistry laboratory of the Leiden University Medical Center [10]. Glomerular filtration rate was estimated by using the CKD-EPI formula [13].

Electrocardiography

Q-waves were assessed using the Minnesota Coding System, a system to objectively describe electrocardiographic findings [14]. This system divides Q waves into three groups based on Minnesota Codes (MC); group 1 codes: 1.1.1 to 1.1.7, group 2 codes: 1.2.1 to 1.2.8 and group 3 codes: 1.3.1 to 1.3.8. In addition, the codes are applied to three groupings of leads namely, I, aVL, V6 (anterolateral), II, III, aVF (inferior) and V1-V5 (anterior). Not every code is present in every group of leads, e.g. 1-2-4 in the inferior leads is not present in the anterior leads and no codes are based on the waveforms in the aVR lead. Examples of different Q-waves (no abnormal Q-wave, borderline Q-wave and large Q-wave) are shown in Supplementary Figure 1. In this study, borderline Q-waves were defined as group 2 and group 3 codes and large Q-waves as group 1 codes.

Abnormal QRS axis was defined as QRS axis < -30° or QRS axis > +90°, minor ST/T abnormalities as MC 4.3, 4.4, 5.3 of 5.4, major ST/T abnormalities as MC 4.1, 4.2, 5.1 or 5.2 and left ventricular hypertrophy as MC 3.1 or 3.2. Percentages of ECG abnormalities in participants without Q-waves and with borderline Q-waves were calculated and the study population was divided in the three groups, namely participants without Q-waves, participants with isolated borderline Q-waves and participants with non-isolated borderline Q-waves. Isolated borderline Q-waves were defined as borderline Q-wave with normal QRS axis, no minor ST/T abnormality, no major ST/T abnormality and no left ventricular hypertrophy and non-isolated as borderline Q-waves plus at least one of these additional abnormalities.

Measures of body fat

Height and weight were measured without shoes and 1 kg was subtracted from the weight to correct for clothing. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Waist circumference was measured with a horizontally placed flexible tape in the middle of the distance between the lowest rib and the iliac crest. Hip circumference was measured at the maximum circumference of the buttocks. Waist-hip-ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. With a bio-impedance device (TBF-310, Tanita International Division, UK) total body fat (TBF) was estimated. Abdominal subcutaneous adipose tissue (aSAT) and visceral adipose tissue (VAT) were assessed by MR imaging (1.5 Tesla MR imaging, Philips Medical Systems) using a turbo spin echo imaging protocol. Three transverse images with a slice thickness of 10 mm were obtained at the level of the fifth lumbar vertebra during a breath-hold. The fat depots were converted from the number of pixels to centimeters squared. In the analyses, the average of the three slices was used.

Measures of subclinical atherosclerosis and vascular stiffness

Carotid intima-media thickness (cIMT) was assessed by ultrasonography of the far wall of the left and right common carotid arteries along a 15 mm long section 10 mm proximal of the bifurcation in recumbent position. A 7.5–10 MHz linear-array transducer (Art.Lab version 2.1, Esaote, Maastricht, The Netherlands) in B-mode setting was used to visualize the distal common carotid arteries and a wall track system was used to detect the lumen-intima and media-adventitia boundaries. The cIMT was measured in three predefined angles per side

(180, 135 and 90 degrees for the right common carotid artery and 180, 225 and 270 degrees for the left common carotid artery) during six heartbeats. Mean cIMT was calculated for each individual by averaging all 36 cIMT measurements within each individual. Velocity-encoded magnetic resonance imaging was used for assessment of pulse wave velocity (PWV) of the aorta. The heart was imaged in short-axis view using an ECG-triggered balanced turbo-field-echo sequence. Data were analysed using in-house software (MASS and FLOW; Leiden University Medical Center, Leiden, the Netherlands).

Statistical analysis

In the NEO study, participants with a BMI of 27 kg/m^2 or higher were oversampled. To correctly represent baseline associations in the general population [15] adjustments for the oversampling of individuals with a BMI 27 kg/m^2 were made. This was done by weighting all participants towards the BMI distribution of participants from the Leiderdorp municipality [16], whose BMI distribution was similar to the BMI distribution of the general Dutch population [17]. All results are based on weighted analysis. Consequently, the results are considered to apply to a population-based study without oversampling of participants with a BMI ≥ 27 kg/m^2.

Baseline characteristics are presented as mean (SD), median (25th, 75th percentiles) or as percentage, for the three specified groups. Next, means (se) of measures of body fat were calculated for each group. Differences with 95% confidence intervals were estimated for the groups with Q-waves compared to the group without Q-waves using linear regression analysis. If differences in BMI, TBF or aSAT were observed between groups, these were adjusted for VAT and if differences in waist circumference or VAT were observed, these were adjusted for TBF. Finally, subclinical atherosclerosis and vascular stiffness were investigated in the three groups and again, differences with 95% confidence intervals were estimated compared with the group without Q-waves. No adjustment for confounding was made since our two study aims were mostly of a descriptive nature. Data were analysed using STATA (Statacorp, College Station, Texas, USA), version 14.

RESULTS

Study groups

681 participants using QT-prolonging drugs were excluded. Similarly, 129 participants with a history of myocardial infarction, 61 with angina pectoris and 6 participants with an artificial pacemaker were excluded. Also, 48 participants with large Q-waves (MC 1.1.x) were excluded. The total number of participants included in this study was 5746, of which 43 % were men. Participants were then divided in participants without Q-waves, with isolated borderline Q-waves and with non-isolated borderline Q-waves. Percentages of other ECG abnormalities in participants without and with borderline Q-waves are shown in Figure 1.

Other ECG abnormalities were more prevalent among participants with borderline compared with no Q-waves. In 16% of participants without Q-waves and in 27% of participants with borderline Q-waves, at least one of the other ECG abnormalities was present. Of the study population, 93.7% did not have Q-waves, 4.6% had isolated borderline Q-waves and 1.7% had non-isolated borderline Q-waves.

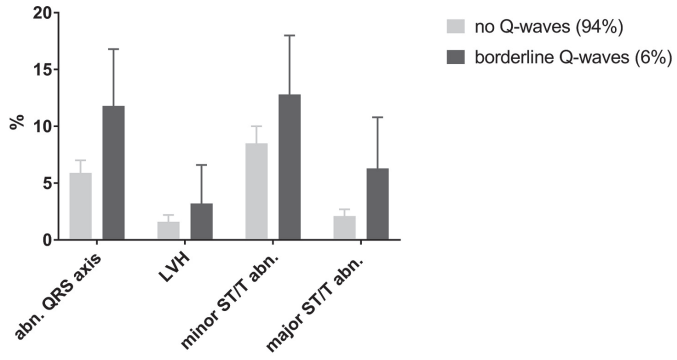

Figure 1. ECG abnormalities in participants without and with borderline Q-waves.
Data are presented as percentages and 95% confidence intervals. Results are based on analyses weighted towards the body mass index distribution of the general population (n=5746).
Abnormal QRS axis: <-30° / >90°; LVH: MC 3.1 , 3.2; minor ST/T abnormality: MC 4.3, 4.4, 5.3, 5.4; major ST/T abnormality: MC 4.1, 4.2, 5.1, 5.2

Baseline characteristics

Baseline characteristics of the three groups (no Q-waves, isolated borderline Q-waves and non-isolated borderline Q-waves) are presented in Table 1. Several risk factors were, compared with participants without Q-waves, higher in participants with isolated borderline Q-waves and highest in participants with non-isolated borderline Q-waves, namely age (55.6, 55.7 and 59.0 years respectively), percentage of men (43, 52 and 61% respectively), systolic (129.9, 131.1 and 137.5 mmHg respectively) as well as diastolic blood pressure (83.1, 83.1 and 86.9 mmHg respectively), use of antihypertensive therapy (20, 23 and 32% respectively), fasting glucose (5.4, 5.6 and 5.7 mmol/l respectively), triglycerides (1.0, 1.0 and 1.2 mmol/l respectively) and use of lipid lowering therapy (8, 13 and 14% respectively). Furthermore, participants with non-isolated borderline Q-waves were less often highly educated (47, 51 and 36% respectively) and had the highest alcohol intake out of the three groups (9.9, 8.8 and 19.2 g/day respectively). No relevant differences were observed in triglyceride, LDL-cholesterol or HDL-cholesterol concentrations or estimated glomerular filtration rate between the groups.

Table 1. Characteristics of 5,746 participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity study

	No Q-waves, 93.7%	Isolated borderline Q-waves, 4.6%	Non-isolated borderline Q-waves, 1.7%
Age, years	55.6 (6.0)	55.7 (6.6)	59.0 (6.5)
Sex, men, %	43	52	61
Ethnicity, white, %	95	99	99
Education level, high, %	47	51	36
Alcohol intake, g/day	9.9 (2.9-21.1)	8.8 (3.2-20.8)	19.2 (7.7-25.0)
Physical activity (MET-hour/week)	30.0 (16.0-50.5)	26.9 (14.0-45.5)	29.0 (17.8-52.0)
Smoking, %			
Never	39	39	22
Former	45	44	68
Current	16	16	10
Body mass index, kg/m^2	25.6 (23.1-28.1)	26.7 (23.7-29.0)	27.4 (24.9-29.9)
Systolic blood pressure, mmHg	129.9 (16.9)	131.1 (18.5)	137.5 (20.3)
Diastolic blood pressure, mmHg	83.1 (10.2)	83.1 (11.6)	86.9 (11.4)
Use of antihypertensive therapy, %	20	23	32
Fasting plasma glucose, mmol/l	5.4 (0.9)	5.6 (1.2)	5.7 (1.3)
Diabetes mellitus, %	5	10	7
Triglycerides, mmol/l	1.0 (0.7-1.4)	1.0 (0.7-1.7)	1.2 (0.7-1.8)
LDL, mmol/l	3.6 (0.9)	3.5 (1.1)	3.6 (1.2)
HDL, mmol/l	1.6 (0.5)	1.5 (0.5)	1.5 (0.6)
Use of lipid lowering therapy, %	8	13	14
eGFR, ml/min/1.73m^2	86.3 (12.3)	86.6 (12.5)	84.9 (13.5)

eGFR, estimated glomerular filtration rate (CKD-EPI); HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; MET, metabolic equivalent of task during leisure time.
Data are presented as mean(SD), median(25th, 75th percentiles), or percentages.
Results were based on analyses weighted towards the BMI distribution of the general population.
Borderline Q-wave: Minnesota codes 1.2.X, 1.3.X
No Q-waves, n=5294; isolated borderline Q-waves, n=317; non-isolated borderline Q-waves, n=135

Table 2. Relations between borderline Q-waves and measures of body fat

	No Q-waves (1), 93.7%	Isolated borderline Q-waves (2), 4.6%	Non-isolated borderline Q-waves (3), 1.7%	Difference 2 vs 1 (95%CI)	p-value*	Difference 3 vs 1 (95%CI)	p-value**
BMI, kg/m^2	26.1 (0.1)	27.1 (0.4)	27.8 (0.5)	1.0 (0.3 - 1.7)	0.006	1.7 (0.7 - 2.8)	0.001
TBF, %	31.5 (0.2)	31.6 (0.7)	31.3 (1.2)	0.2 (-1.3 - 1.6)	0.828	-0.2 (-2.6 - 2.1)	0.855
aSAT, cm^2	232.0 (2.5)	238.9 (12.8)	254.0 (21.8)	7.0 (-18.5 - 32.5)	0.593	22.1 (-21.0 - 65.1)	0.315
Waist circ., cm	91.4 (0.2)	94.8 (1.2)	96.9 (1.7)	3.4 (1.0 - 5.8)	0.005	5.5 (2.2 - 8.8)	0.001
VAT, cm^2	86.6 (1.5)	108.5 (7.2)	115.9 (10.8)	21.9 (7.4 - 36.3)	0.003	29.3 (7.8 - 50.7)	0.007
WHR	0.88 (0.00)	0.90 (0.01)	0.92 (0.01)	0.01 (-0.00 - 0.03)	0.098	0.03 (0.01 - 0.05)	0.001

aSAT, abdominal subcutaneous adipose tissue; BMI, Body Mass Index; TBF, total body fat; VAT, visceral adipose tissue; Waist circ., waist circumference; WHR, waist:hip ratio.
Data are presented as mean (se) and difference (95% confidence interval).
Results are based on linear regression analyses weighted towards the BMI distribution of the general population. For VAT and aSAT: no Q-waves n = 2099; isolated borderline Q-waves n = 121; non-isolated borderline Q-waves n = 50.
* 2 vs 1, ** 3vs 1

Table 3. Relations between borderline Q-waves and subclinical atherosclerosis and vascular stiffness

	No Q-waves (1), 93.7%	Isolated borderline Q-waves (2), 4.6%	Non-isolated borderline Q-waves (3), 1.7%	Difference 2 vs 1 (95%CI)	p-value*	Difference 3 vs 1 (95%CI)	p-value**
PWV, m/s	6.6 (0.0)	6.3 (0.1)	7.8 (0.4)	-0.2 (-0.5 - 0.1)	0.139	1.2 (0.4 - 2.0)	0.004
cIMT, µm	614.7 (1.9)	617.4 (6.8)	638.1 (10.2)	2.7 (-11.2 - 16.5)	0.704	23.4 (3.0 - 43.8)	0.024

cIMT, carotid intima media thickness; PWV, pulse wave velocity.
Data are presented as mean (se) or difference (95% confidence interval)
Results are based on linear regression analyses weighted towards the BMI distribution of the general population.
For PWV: no Q-waves n = 2032; borderline isolated Q-waves n = 119; non-isolated borderline Q-waves n = 45. For cIMT: no Q-waves n = 5233; borderline isolated Q-waves n = 313; non-isolated borderline Q-waves n = 135.
* 2 vs 1, ** 3vs 1.

Borderline Q-waves and measures of body fat

Table 2 reports measures of body fat in the three groups. For measures of body fat, participants with isolated borderline Q-waves had a higher BMI (difference: 1.0 kg/m^2; 95% confidence interval: 0.3 - 1.7; p-value 0.006), higher waist circumference (3.4 cm; 1.0 - 5.8; 0.005), and more VAT (21.9 cm^2; 7.4 - 36.3; 0.003) compared with participants without Q-waves. The difference of measures of body fat for participants with non-isolated borderline Q-waves compared with participants without Q-waves was even larger (BMI: 1.7 kg/m^2; 0.7 - 2.8; 0.001; waist circumference: 5.5 cm; 2.2 - 8.8; 0.001; VAT: 29.3 cm^2; 7.8 - 50.7; 0.007; WHR: 0.03; 0.01 - 0.05; 0.001). There were no differences between participants with isolated or non-isolated borderline Q-waves and participants without Q-waves for TBF and aSAT. Furthermore, the difference in BMI between groups disappeared after adjusting for VAT (isolated borderline Q-waves compared with no Q-waves: -0.2 kg/m^2; -0.9 - 0.6; 0.620 and non-isolated borderline Q-waves compared with no Q-waves: 1.1 kg/m^2; -0.3 - 2.4; 0.134), while the difference in waist circumference and VAT between groups remained after adjusting for TBF.

Borderline Q-waves and subclinical atherosclerosis and vascular stiffness

In Table 3 measures of subclinical atherosclerosis and vascular stiffness are shown in the three groups. The differences between participants with isolated borderline Q-waves and participants without Q-waves were small for both PWV (-0.2 m/s; -0.5 - 0.1; 0.139) and cIMT (2.7 µm; -11.2 - 16.5; 0.704). However, participants with non-isolated borderline Q-waves had a higher PWV (difference: 1.2 m/s; 95%CI: 0.4 - 2.0; 0.004) as well as higher cIMT (23.4 µm; 3.0 - 43.8; 0.024) compared with participants without Q-waves.

DISCUSSION

In this cross-sectional analysis of 5746 participants of the NEO study, we observed, compared with participants without Q-waves, a worse cardiovascular risk profile in participants with isolated borderline Q-waves, that was even worse in participants with non-isolated borderline Q-waves. Participants with non-isolated borderline Q-waves, compared with participants without Q-waves were older, more often male, had a higher alcohol intake and also higher blood pressure and fasting glucose concentrations. For participants with isolated borderline Q-waves, compared with participants without Q-waves, cardiovascular risk factors were more often present, however, less evident than for participants with non-isolated borderline Q-waves. This association between cardiovascular risk factors and borderline Q-waves is in line with literature, although reports vary in the exact risk factors associated with borderline Q-waves [4-6]. Borderline Q-waves could be the result of scar tissue, in which no electrical activity is present, representing damage to the heart tissue.

We observed higher values of several measures of body fat (BMI, waist circumference, VAT and WHR) in participants with isolated borderline Q-waves and the highest values in participants with non-isolated borderline Q-waves, compared with participants without Q-waves. No differences were observed for TBF or aSAT. Two previous studies report no differences in BMI between individuals with borderline Q-waves and without [4,6]. In the general population-

based 4th Copenhagen City Heart Study mean BMI in 5627 individuals without Q-waves was 25.7 kg/m^2, whereas this was 26.3 kg/m^2 in 114 individuals with Q-waves (defined as MC 1.1.X to 1.3.X) [4]. Despite this difference not being statistically significant, similar to our study, individuals with Q-waves have a higher BMI than individuals without Q-waves. Furthermore, a study in the general Japanese population did not observe differences in BMI between individuals without abnormal Q-waves (men: 22.5 kg/m^2, women: 22.8 kg/m^2), individuals with mild abnormal Q-waves (defined as MC 1.3.X; men: 22.9 kg/m^2, women: 23.0 kg/m^2) and individuals with moderate/severe abnormal Q-waves (defined as MC 1.2.X or 1.1.X; men: 22.1 kg/m^2, women: 24.4 kg/m^2) [6]. In this Japanese population the BMI of individuals is generally lower than the BMI of Dutch individuals included in the NEO study, which makes it difficult to compare these results to our study.

Our results are plausible, since overweight/obesity is an important cardiovascular risk factor. Since both waist circumference and VAT are measures of abdominal adiposity and no differences were observed for TBF between groups, we also investigated whether differences in BMI between groups were mainly due to differences in abdominal adiposity. Indeed, the difference in BMI between groups disappeared after adjustment for waist circumference or VAT, indicating that differences in abdominal adiposity between the three groups are also responsible for the observed BMI difference.

Finally, we observed that PWV and cIMT, measures of subclinical atherosclerosis and vascular stiffness, were higher in participants with non-isolated borderline Q-waves than in participants without Q-waves, but that this was less clear for isolated borderline Q-waves. This association of non-isolated borderline Q-waves with more subclinical atherosclerosis and vascular stiffness is in line with the increased prevalence of cardiovascular risk factors, the presence of other ECG abnormalities, and more abdominal adiposity.

The fact that borderline Q-waves are associated with specifically higher amounts of VAT gives more insight into the cardiovascular risk associated with these borderline Q-waves. Several underlying pathways are thought to be involved in these associations. Visceral adipocytes have high lipolytic activity and cause an increased amount of free fatty acids to be released into the portal circulation, leading to hepatic insulin resistance and adverse cardiovascular effects [18-20]. Furthermore, VAT is a metabolically active tissue, secreting several cytokines, chemokines and hormones, and has been linked to several unfavorable conditions, such as insulin resistance, impaired lipid and glucose metabolism, CVD and mortality [21-24]. More VAT is also accompanied by higher concentrations of pro-inflammatory factors, such as interleukin 6, tumor necrosis factor-α and C-reactive protein, that can enhance a local pro-inflammatory environment, but also can have more systemic effects, promoting atherosclerotic disease and arterial stiffness [7, 25-30]. Also, associations between VAT and more subclinical atherosclerosis and vascular stiffness have been shown in the literature and abdominal adiposity has been described as a stronger risk factor for subclinical atherosclerosis and vascular stiffness than overall adiposity [31-33].

In current practice, borderline isolated Q-waves are often considered as non-pathological. However, the appearance of a borderline isolated Q-wave on the ECG of an individual without known CVD could represent electrical damage, an unrecognized myocardial infarction, and be associated with a worse prognosis [34]. Especially the presence of a 1.2 coded borderline Q-wave together with T wave changes, could be the result of an unrecognized myocardial infarction, which was associated with poor prognosis previously [35,36]. The borderline Q-wave could also just be a positional variant, without any prognostic consequences, which makes clinical decision making particularly complicated.

Borderline Q-waves could possibly improve current risk prediction scores for CVD. In 6991 individuals from the Copenhagen Heart Study aged 65 and over, ECG changes among which abnormal Q-waves, showed added value in the prediction of fatal and non-fatal cardiovascular events [37]. Future studies should further elucidate the role of borderline Q-waves in cardiovascular risk prediction.

In this study we observed a worse cardiovascular risk factor profile as well as higher waist circumference and VAT in participants with isolated borderline Q-waves, which was even more pronounced in participants with non-isolated borderline Q-waves, compared with participants without Q-waves. We also observed non-isolated, but not isolated borderline Q-waves to be associated with more subclinical atherosclerosis and vascular stiffness, compared with no Q-waves. Therefore it would be of great interest to investigate the association of borderline Q-waves with cardiovascular risk within certain subgroups of individuals with increased cardiometabolic risk. Future studies should investigate whether it might be indicated to further investigate borderline Q-waves when found on an individual's ECG, especially in individuals with increased waist circumference or VAT, who already are at higher cardiovascular risk.

Strengths and limitations

The largest strength of this study is the extensive phenotyping of a large number of participants, which made it possible to investigate several different measures of body fat and subclinical atherosclerosis and vascular stiffness in relation to borderline Q-waves. There are also some limitations of this study that need to be considered. In this study, only 4.6% of participants displayed isolated borderline Q-waves on the ECG and 1.7% of participants non-isolated borderline Q-waves. Subgroups of participants with increased cardiovascular risk, or increased waist circumference or VAT were too small and therefore we did not have enough statistical power to investigate the association of borderline Q-waves with subclinical atherosclerosis and vascular stiffness within subgroups. However, the prevalence of borderline Q-waves observed in this present study is similar to the prevalence in other population-based studies [4,6]. Also, it should be noted that coding ECGs according to the Minnesota Coding system is not error-free. Measurement error is likely to be also present in this study, e.g. if wrongly measured, a 1.2 code could actually be a 1.1 or 1.3 code.

Conclusion

The results of this study show an unfavorable cardiometabolic risk factor profile in participants with isolated borderline Q-waves that is even more unfavorable in participants with non-isolated borderline Q-waves. Furthermore, measures of abdominal adiposity, namely waist circumference and VAT, were higher in participants with isolated borderline Q-waves and highest in participants with non-isolated borderline Q-waves, compared with participants without Q-waves. Also, non-isolated borderline Q-waves were associated with more subclinical atherosclerosis and vascular stiffness, results for isolated borderline Q-waves are less clear, despite the less favourable cardiometabolic risk factor profile.

Borderline Q-waves can be identified on an easily obtainable ECG, which makes them a possibly useful addition to cardiovascular risk assessment. The possible added value of borderline Q-waves to current risk prediction scores for CVD should be further investigated in future studies. Furthermore, the prognostic significance of borderline Q-waves within subgroups of individuals with increased cardiovascular risk or with more body fat could be investigated in longitudinal studies.

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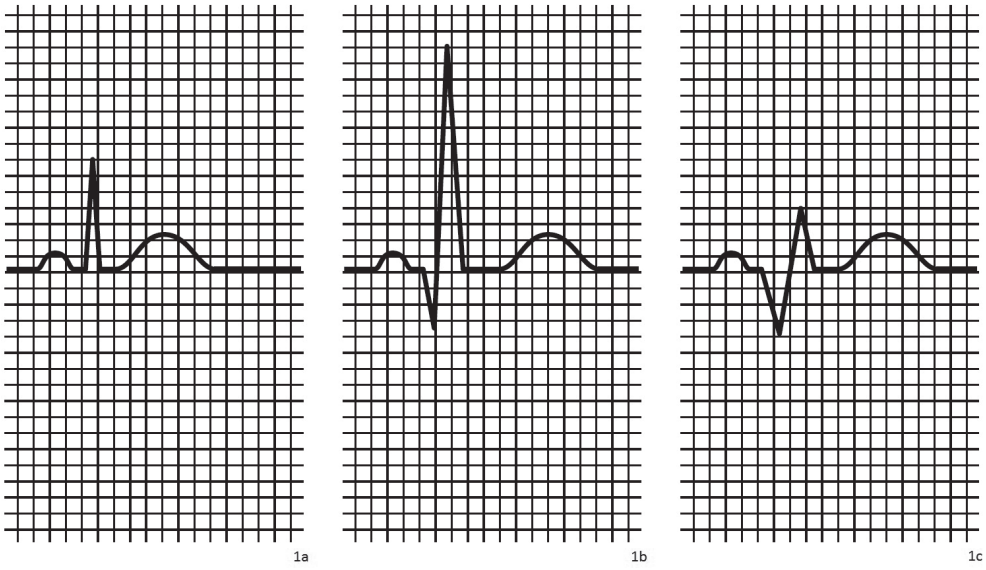
We express our gratitude to all individuals who participate in the Netherlands Epidemiology in Obesity study. We are grateful to all participating general practitioners for inviting eligible participants. We furthermore thank P.R. van Beelen and all research nurses for collecting the data, P.J. Noordijk and her team for sample handling and storage, and I. de Jonge, MSc for data management of the NEO study.



Supplementary Figure 1. Examples of different Q-waves [14].

a. No abnormal Q-wave in lead I.

b. Minnesota code 1–2-2: Q duration ≥0.03 s and <0.04 s in lead I, II, or V2-V6, Q/R ratio <1/3.

c. Minnesota code 1–1-5: Q duration ≥0.05 s in lead aVF.

REFERENCES

1. Kligfield P, Gettes LS, Bailey JJ, Childers R, Deal BJ, Hancock EW, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part I: The electrocardiogram and its technology: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation. 2007;115:1306-24.
2. Mason JW, Hancock EW, Gettes LS, Bailey JJ, Childers R, Deal BJ, et al. Recommendations for the standardization and interpretation of the electrocardiogram: part II: Electrocardiography diagnostic statement list: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. Circulation. 2007;115:1325-32.
3. Davis TME, Fortun P, Mulder J, Davis WA, Bruce DG. Silent myocardial infarction and its prognosis in a community-based cohort of type 2 diabetic patients: the fremantle diabetes study. Diabetologia. 2004; 47:395–399.
4. Godsk P, Jensen JS, Abildstrom SZ, Appleyard M, Pedersen S, Mogelvang R. Prognostic significance of electrocardiographic Q-waves in a low-risk population. Europace. 2012;14:1012-7.
5. Li Y, Dawood FZ, Chen H, Jain A, Walsh JA 3rd, Alonso A, et al. Minor isolated Q waves and cardiovascular events in the MESA study. Am j Med. 2013;126:450 e9- e16.
6. Higashiyama A, Hozawa A, Murakami Y, Okamura T, Watanabe M, Nakamura Y, et al. Prognostic value of q wave for cardiovascular death in a 19-year prospective study of the Japanese general population. J Atheroscler Thromb. 2009;16:40-50.
7. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444:881-7.
8. Staiano AE, Reeder BA, Elliott S, Joffres MR, Pahwa P, Kirkland SA, et al. Body mass index versus waist circumference as predictors of mortality in Canadian adults. Int J Obes. 2012;36:1450-4.
9. Recio-Rodriguez JI, Gomez-Marcos MA, Patino-Alonso MC, Agudo-Conde C, Rodriguez-Sanchez E, Garcia-Ortiz L, et al. Abdominal obesity vs general obesity for identifying arterial stiffness, subclinical atherosclerosis and wave reflection in healthy, diabetics and hypertensive. BMC Cardiovasc Disord. 2012;12:3.
10. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013;28:513-23.
11. Verkleij-Hagoort AC, de Vries JH, Stegers MP, Lindemans J, Ursem NT, Steegers-Theunissen RP. Validation of the assessment of folate and vitamin B12 intake in women of reproductive age: the method of triads. Eur J Clin Nutr 2007;61:610-5.
12. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J Clin Epidemiol. 2003;56:1163-9.
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-12.
14. Prineas RJ CR, Blackburn HW. The Minnesota Code Manual of Electrocardiographic Findings: Standards and Procedures for Measurement and Classification. J Wright; Boston, MA. 1982.

15. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health. 1991;81:1166-73.
16. Lumley T. Analysis of complex survey samples. J Stat Softw. 2004; 9:1-19.
17. Ministerie van VWS. Hoeveel mensen hebben overgewicht? NdMG. 2014.
18. Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. Obesity. 2006;14 Suppl 1:16S-9S.
19. Bjorntorp P. "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. Arteriosclerosis. 1990;10:493-6.
20. Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD. Splanchnic lipolysis in human obesity. J Clin Invest. 2004;113:1582-8.
21. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007;116:39-48.
22. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. Lancet. 2005;366:1640-9.
23. Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L. Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. Br Med J (Clin Res Ed). 1984;289:1257-61.
24. Despres JP. Is visceral obesity the cause of the metabolic syndrome? Ann Med. 2006;38:52-63.
25. Raggi P. Epicardial adipose tissue as a marker of coronary artery disease risk. J Am Coll Cardiol. 2013;61:1396-7.
26. Apovian CM, Bigornia S, Mott M, Meyers MR, Ulloor J, Gagua M, et al. Adipose macrophage infiltration is associated with insulin resistance and vascular endothelial dysfunction in obese subjects. Areterioscler Thromb Vasc Biol. 2008;28:1654-9.
27. Wajchenberg BL, Giannella-Neto D, da Silva ME, Santos RF. Depot-specific hormonal characteristics of subcutaneous and visceral adipose tissue and their relation to the metabolic syndrome. Horm Metab Res. 2002;34:616-21.
28. de Heredia FP, Gomez-Martinez S, Marcos A. Obesity, inflammation and the immune system. Proc Nutr Soc. 2012;71:332-8.
29. Park S, Lakatta EG. Role of inflammation in the pathogenesis of arterial stiffness. Yonsei Med J. 2012;53:258-61.
30. Hajjar DP, Gotto AM, Jr. Biological relevance of inflammation and oxidative stress in the pathogenesis of arterial diseases. Am J Pathol. 2013;182:1474-81.
31. Lear SA, Humphries KH, Kohli S, Frohlich JJ, Birmingham CL, Mancini GB. Visceral adipose tissue, a potential risk factor for carotid atherosclerosis: results of the Multicultural Community Health Assessment Trial (M-CHAT). Stroke. 2007;38:2422-9.
32. Gast KB, den Heijer M, Smit JW, Widya RL, Lamb HJ, de Roos A, et al. Individual contributions of visceral fat and total body fat to subclinical atherosclerosis: The NEO study. Atherosclerosis. 2015;241:547-54.
33. Strasser B, Arvandi M, Pasha EP, Haley AP, Stanforth P, Tanaka H. Abdominal obesity is associated with arterial stiffness in middle-aged adults. Nutr Metab Cardiovasc Dis. 2015;25:495-502.
34. Sheifer SE, Gersh BJ, Yanez ND 3rd, Ades PA, Burke GL, Manolio TA. Prevalence, predisposing factors, and prognosis of clinically unrecognized myocardial infarction in the elderly. J Am Coll Cardiol. 2000;35:119-26.

35. Kwong RY, Sattar H, Wu H, Vorobiof G, Gandla V, Steel K, et al., Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. Circulation. 2008;118:1011–1020.
36. Schelbert EB, Cao JJ, Sigurdsson S, Aspelund T, Kellman P, Aletras AH, et al. Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. JAMA. 2012;308:890-6.
37. Jorgensen PG, Jensen JS, Marott JL, Jensen GB, Appleyard M, Mogelvang R. Electrocardiographic changes improve risk prediction in asymptomatic persons age 65 years or above without cardiovascular disease, J Am Coll Cardiol. 2014;64:898–906.

CHAPTER 6

Carotid intima media thickness, pulse wave velocity and the spatial QRS-T angle

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ABSTRACT

Background

The spatial QRS-T angle (spQRSTa) reflects ventricular electrophysiological heterogeneity and has previously been studied as prognostic factor for cardiovascular events and mortality. To gain more insight in mechanisms involved in spQRSTa widening, we investigated associations between a) several cardiovascular risk factors; b) carotid intima-media thickness (cIMT), as a marker of subclinical atherosclerosis; c) pulse wave velocity (PWV), as a marker of arterial stiffness, and the spQRSTa. Also, we wished to investigate the ability of spQRSTa to discriminate between normal and high cIMT or high PWV.

Methods

We performed cross-sectional analyses within the Netherlands Epidemiology of Obesity (NEO) study cohort (n=6671). Participants with electrocardiographic evidence of atrial flutter, fibrillation or other arrhythmias were excluded, as well as participants with missing spQRSTa measurements. SpQRSTa was determined from 12-lead electrocardiograms, cIMT was assessed with ultrasonography and PWV was determined with velocity-encoded magnetic resonance imaging. Risk factors were assessed over three groups of spQRSTa, based on sex-specific percentiles (<p75, p75-p95, >p95). Associations of cIMT and PWV with spQRSTa were investigated with linear regression analysis. Ability of spQRSTa to discriminate between normal and high (>p75, p95 or p99) cIMT or PWV was assessed using the area under the receiver operating characteristic curve.

Results

We included 6342 participants, of whom 6278 had cIMT and 2369 had PWV measurements. Several cardiovascular risk factors were associated with a wider spQRSTa. Compared with participants with a normal glucose metabolism (mean spQRSTa: 54°), spQRSTa was wider in participants with impaired (58°) or high (66°) fasting glucose, or type II diabetes mellitus (61°). Furthermore, both greater cIMT and PWV were associated with a wider spQRSTa in crude models (difference in spQRSTa per SD cIMT: 2.7°, 95%CI: 1.6 - 3.8; per SD PWV: 2.9°, 1.3 - 4.4), but not in models adjusted for classical cardiovascular risk factors (cIMT: 0.5°, -0.7 -1.6; PWV: 0.6°, -1.3- 2.4). Addition of spQRSTa to the variables age, sex, BMI, systolic blood pressure and smoking did not improve discriminative ability for either cIMT or PWV.

Conclusions

Several cardiovascular risk factors were associated with spQRSTa, and a wider angle was found in participants with impaired fasting glucose or type II diabetes mellitus, compared with normal glucose metabolism. Furthermore, associations between greater cIMT and PWV and wider spQRSTa were present. These findings may partly explain the fact that spQRSTa, an electrocardiographically and cheaply determinable variable, is a prognostic factor for cardiovascular morbidity and mortality.

INTRODUCTION

The spatial QRS-T angle (spQRSTa) can be computed from a regular electrocardiogram (ECG) and can be used to assess overall heterogeneity of the ventricular action potential morphology. A wider spQRSTa reflects a more heterogeneous or abnormal repolarization of the ventricles, or ventricular electrophysiological heterogeneity. Several cardiovascular risk factors have been associated with a wider spQRSTa [1-7]. In individuals with type II diabetes mellitus (T2DM), the spQRSTa has been reported to be wider, and a wider spQRSTa has also been associated with poorer glycaemic control [7]. An abnormal spQRSTa is the result of changes in action potential duration in certain areas of the heart. These changes in action potential duration can be the result of, amongst others infarction, ischemia, or fibrosis and can ultimately lead to arrhythmias and cardiovascular events [8,9]. The spQRSTa has already gained recognition as a prognostic factor for cardiovascular events and mortality in several populations [3,6,10-15]. However, little is known of the associations between subclinical atherosclerosis or arterial stiffness and the spQRSTa. Since an abnormal spQRSTa could be the result of damaged areas of the myocardium, associations of subclinical atherosclerosis and arterial stiffness with the spQRSTa are plausible. In peritoneal dialysis patients, both intima-media thickness and coronary artery calcification were predictors of wider spQRSTa, even when classical cardiovascular risk factors were taken into account [16]. This study aimed to identify cardiovascular risk factors associated with a wider spQRSTa in a large study population. Furthermore, we explored associations between subclinical atherosclerosis and arterial stiffness and spQRSTa. When such associations were present, we investigated whether they remained present after adjustment for known cardiovascular risk factors. The spQRSTa can be derived from the ECG, which is widely used and easily obtainable in clinical practice, whereas carotid intima-media thickness (cIMT) and pulse wave velocity (PWV) are less easily measured. Therefore, we investigated the added value of the spQRSTa, as a marker of underlying cardiovascular pathology, in cardiovascular risk prediction by investigating the ability of spQRSTa to discriminate between normal and high cIMT or high PWV.

METHODS

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a prospective, population-based cohort study with 6671 participants included between 2008 and 2012. Men and women aged between 45 and 65 years living in the area of greater Leiden (the Netherlands) and with a BMI ≥27 kg/m^2 were eligible to participate. In addition, all inhabitants aged between 45 and 65 years from one municipality (Leiderdorp) were invited to join irrespective of their BMI, allowing for a reference distribution of BMI. Participants completed a questionnaire on demographic and clinical information prior to the visit to the NEO study center. Participants were invited to a baseline visit at the NEO study centre after an overnight fast. Participants with ECG evidence of atrial, junctional or ventricular premature beats, atrial flutter or fibrillation, and other arrhythmias were excluded (n=237). Also participants with missing spQRSTa values were excluded (n=92). More information on the study design and population has been published elsewhere [17]. The Medical Ethics Committee of the Leiden University

Medical Center (LUMC) approved the design of the study. All participants gave their written informed consent.

Ethnicity was self-reported in eight categories on the questionnaire and then grouped into white and other. Education level was grouped as low (none, primary school or lower vocational education) and high education (intermediate secondary education, middle-level vocational education, higher secondary education, higher professional education, university or other). Tobacco smoking was categorized into current, former, or never smokers. Participants were asked to bring all medication they were currently using to the study visit. Height and weight were measured without shoes and 1 kg was subtracted from the weight to correct for the weight of clothing. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Brachial blood pressure was measured in a seated position on the right arm using a validated automatic oscillometric device (OMRON, Model M10-IT, Omron Health Care Inc, IL, USA). Blood pressure was measured three times with 5 minutes rest between consecutive measurements. The mean systolic and diastolic blood pressure was calculated. Blood samples were drawn after an overnight fast of 10 hours. Fasting glucose, triglyceride, total cholesterol and high-density lipoprotein cholesterol concentrations were measured with the enzymatic colorimetric method (Roche Modular Analytics P800, Roche Diagnostics Mannheim, Germany). Low-density lipoprotein cholesterol concentrations were calculated using the Friedewald equation.

Categories of glucose metabolism

We defined four categories of glucose metabolism. I): Normal glucose metabolism, defined as fasting plasma glucose concentration <6.1 mmol/l and no self-reported T2DM or medication use. II): Impaired fasting glucose, defined as fasting plasma glucose concentration 6.1-7.0 mmol/l and no self-reported T2DM or medication use. III): High fasting plasma glucose, defined as fasting plasma glucose concentration ≥7.0 mmol/l and no self-reported T2DM or medication use. IV): T2DM, defined as self-reported T2DM or medication use for diabetes mellitus.

Electrocardiography

A 12-lead resting ECG was obtained using a Mortara Eli-350 electrocardiograph (Mortara Instrument Inc., Milwaukee, WI, USA) after a resting period of at least 10 minutes. ECGs were stored in a MegaCare ECG management system (Dräger, formerly Siemens). The raw data were extracted and transferred to the University of Glasgow ECG core lab where ECGs were automatically processed and Minnesota codes were assigned using the University of Glasgow ECG analysis program [18]. Moreover, standard 10-second ECGs were stored in an 8-lead (I, II, V1-V6), 5000 sample comma-separated-value file. The Kors matrix was used to calculate vector cardiograms from the eight independent ECG leads [19]. ECGs and vector cardiograms were analyzed using the automatic MATLAB-based (The MathWorks, Natick, MA) program BEATS and the semiautomatic program LEADS [20,21]. BEATS was used to detect the timings of all QRS complexes and calculated R-R intervals (ms). The QRS and T integral vectors were approximated by calculating the numerical sum of x-y-z deflections (amplitudes of positive deflections are added and those of negative deflections subtracted). The spatial

QRS-T angle was defined as the angle (°) between the integral QRS vector and the integral T vector. In a subgroup (n=962), spQRSTa was assessed by two researchers, with an intraclass correlation coefficient (95% CI) of 0.99 (0.98 - 0.99).

Measures of atherosclerosis and arterial stiffness

Carotid intima-media thickness was assessed by ultrasonography of the far wall of the left and right common carotid arteries along a 15 mm long section 10 mm proximal to the bifurcation in recumbent position. A 7.5–10 MHz linear-array transducer (Art.Lab version 2.1, Esaote, Maastricht, The Netherlands) in B-mode setting was used to visualize the distal common carotid arteries and a wall track system was used to detect the lumen-intima and media-adventitia boundaries. The cIMT was measured in three predefined angles per side (180, 135 and 90 degrees for the right common carotid artery and 180, 225 and 270 degrees for the left common carotid artery) during six heartbeats. Mean cIMT was calculated for each individual by averaging all 36 cIMT measurements within each individual.

PWV of the aorta was assessed in a random group of 30% of all NEO study participants without contraindications for magnetic resonance imaging (most notably metallic devices, claustrophobia, or a body circumference of more than 1.70 m). PWV was determined on a 1.5 Tesla (T) whole-body MRI scanner (Gyroscan ACS/NT15, Philips, Best, the Netherlands) using multi-slice, two-one-directional in-plane velocity-encoded MRI. PWV was calculated by the ratio of the distance along the aortic center line (Δx) and the transit-time of the propagating systolic pulse wave between two measurement sites (Δt) (proximal aorta and distal aorta summed). The heart was imaged in short-axis view using an ECG-triggered balanced turbo-field-echo sequence. Data were analysed using in-house software (MASS and FLOW; Leiden University Medical Center, Leiden, the Netherlands).

Statistical analyses

In the NEO study, participants with a BMI of 27 kg/m^2 or higher were oversampled. To correctly represent baseline associations in the general population [22], adjustments for the oversampling of participants with a BMI ≥ 27 kg/m^2 were made. This was done by weighting all participants towards the BMI distribution of participants from the Leiderdorp municipality [23], whose BMI distribution was similar to the BMI distribution of the general Dutch population [24]. All results are based on weighted analysis. Consequently, the results are considered to apply to a population-based study without oversampling of participants with a BMI ≥ 27 kg/m^2.

The baseline characteristics of study participants were presented as mean (SD) or percentage in Table 1. Since one of the study aims was to describe cardiovascular risk factors associated with a wider spQRSTa, characteristics of the participant are also presented stratified by three groups of spQRSTa in Table 1. The three groups of spQRSTa were based on sex-specific percentiles, namely <75th percentile (<p75, representing a normal spQRSTa), 75-95th percentile (p75-p95 representing a borderline abnormal spQRSTa) and >95th percentile (>p95 representing an abnormal spQRSTa). For men, <p75 corresponded with spQRSTa <76.0° and >p95 corresponded with spQRSTa > 119.8°. For women, <p75 corresponded with spQRSTa

<63.9° and >p95 corresponded with spQRSTa > 103.4°. Mean spQRSTa was determined for the four glucose metabolism categories as described above. Then, associations between cIMT and PWV and spQRSTa were investigated in the whole study population and in men and in women separately, with weighted linear regression analyses, and were expressed as difference (95% CI) in spQRSTa (°) per standard deviation (SD) increase in cIMT (mm) or PWV (m/s). Furthermore, the ability of spQRSTa to discriminate between normal and high cIMT or PWV was assessed using the area under the receiver operating characteristic curve (AUC). To define normal/high cIMT and PWV, both liberal and more conservative cut-offs were used, namely p75, p95 and p99. AUC was also assessed for a combination of simple risk factors, namely age, sex, BMI, systolic blood pressure and smoking, and it was investigated whether addition of the spQRSTa to these variables led to improvement of the AUC. Data were analysed using STATA (Statacorp, College Station, Texas, USA) version 14.

RESULTS

Participants with ECG evidence of atrial, junctional or ventricular premature beats, atrial flutter or fibrillation, and other arrhythmias were excluded (n=237). Also 92 participants with missing spQRSTa values were excluded. The baseline characteristics of the 6342 included participants are presented in Table 1, over three groups of the spQRSTa (<p75, p75-p95 and >p95). SpQRSTa increased with increasing age, HbA1c, use of glucose lowering medication, systolic and diastolic blood pressure, use of antihypertensive therapy and use of lipid lowering medication.

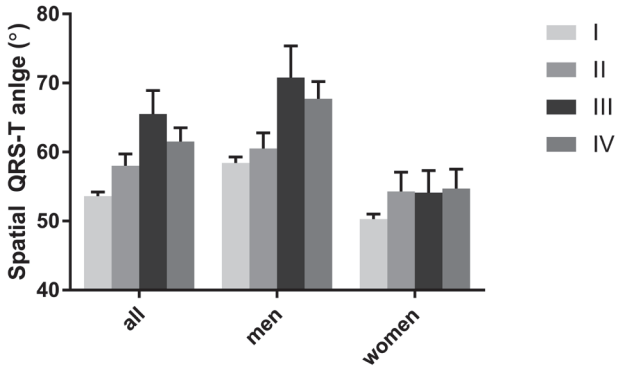

Figure 1. Mean spatial QRS-T angle over the different glucose metabolism categories

All results are based on analyses weighted towards the body mass index distribution of the general population. Data are presented as mean(se)
Glucose metabolism categories I: no diabetes mellitus and fasting glucose<6.1 mmol/l, II: fasting glucose 6.1-7.0 mmol/l, III: fasting glucose >7.0 mmol/l and no diabetes mellitus or use of glucose lowering medication, IV: type II diabetes mellitus or use of glucose lowering medication
All: category I, n=4908; II, n=727; III, n=206; IV, n=423. Men: I, n=2171; II, n=420; III, n=121; IV, n=227. Women : I, n=2737; II, n=307; III, n=85; IV, n=196

Table 1. Baseline characteristics of 6342 participants aged 45-65 years from the Netherlands Epidemiology of Obesity study population

		Spatial QRS-T angle		
	All, 100%	<p75(1)	p75-p95 (2)	>p95 (3)
Age, years	56 (6)	55 (6)	56 (6)	58 (6)
Sex, men, %	43	43	43	44
Ethnicity, white, %	95	95	93	97
Education, high, %	46	46	46	40
Current smoking, %	16	15	18	17
BMI, kg/m2	26.3 (4.4)	26.2 (4.2)	26.6 (4.9)	27.2 (5.7)
Fasting glucose, mmol/l	5.5 (1.0)	5.4 (0.9)	5.5 (1.1)	5.7(1.2)
HbA1c, %	5.4 (0.5)	5.3 (0.4)	5.4 (0.6)	5.5 (0.6)
Glucose-lowering medication, %	3	2	4	5
Systolic blood pressure, mmHg	130.2 (17.0)	129.1 (16.1)	132.5 (19.2)	136.5 (19.3)
Diastolic blood pressure, mmHg	83.2 (10.3)	82.6 (9.9)	84.8 (11.3)	85.3 (10.7)
Use of antihypertensive therapy, %	23	21	29	36
LDL-cholesterol, mmol/l	3.5 (1.0)	3.6 (0.9)	3.5 (1.0)	3.5 (1.1)
Triglycerides, mmol/l	1.2 (0.9)	1.2 (0.8)	1.3 (0.9)	1.3 (0.8)
Use of lipid lowering medication, %	11	9	13	18

BMI, body mass index; HbA1c, glycated haemoglobin; LDL-cholesterol, low-density lipoprotein cholesterol; p, percentile. Data are presented as mean (SD), percentages or difference (95% confidence interval)
Results are based on analyses weighted towards the body mass index distribution of the general population <p75, n=4570; p75-p95, n=1401; >p95, n=371

As shown in Figure 1, the mean spQRSTa increased across glucose metabolism categories I, II and III in the total study population (from 54° to 58° to 66°), in men (from 58° to 60° to 71°), and in a less pronounced way in women (from 50° to 54° to 54°). Mean (SD) spQRSTa in glucose metabolism category IV was 61° (34) in all, 68° (42) in men and 55° (42) in women.

Measurements of cIMT and PWV were available in 6278 and 2369 participants, respectively. As shown in Figure 2, in the total group, greater cIMT was associated with wider spQRSTa in the crude model 1 (difference in spQRSTa per SD increase in cIMT: 2.7°; 95% CI: 1.6 -- 3.8) and in the sex and age-adjusted model 2 (1.1°; 95% CI: 0.0 - 2.3), but, as was expected, not in model 3 adjusted for classical cardiovascular risk factors (0.5°; 95% CI: -0.7- 1.6). In men, associations were somewhat stronger than in women, e.g., in model 1 in men the difference in spQRSTa per SD increase in cIMT was 3.0° (95%CI: 1.3- 4.8) and in women this was 1.2° (95%CI: -0.2 - 2.6). Also, in men no association was present between cIMT and spQRSTa in model 3. Furthermore, higher PWV was associated with a wider spQRSTa in the total group in model 1 (difference in spQRSTa per SD increase in PWV: 2.9°; 95% CI: 1.4 - 4.4) and in

model 2 (2.1°; 95% CI: 0.3 - 3.9), but not in model 3 (0.6°; 95% CI: -1.3 - 2.4). When the study group was stratified by sex, we found in men that PWV was associated with the spQRSTa in model 3 (2.6°; 95% CI: 0.0 - 5.2), whereas this association was not present in women (-0.7°; 95% CI: -3.4 - 1.9).

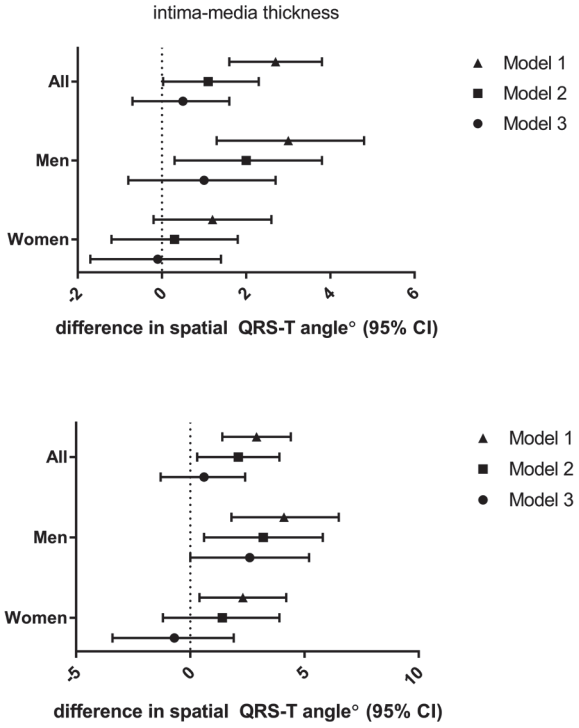

Figure 2. Associations of carotid intima-media thickness and pulse wave velocity with the spatial QRS-T angle in all, in men and in women
Results are presented as difference (95% confidence interval) per standard deviation increase in carotid intima-media thickness or pulse wave velocity. All results are based on analyses weighted towards the body mass index distribution of the general population.
Model 1: crude, model 2: adjusted for age (and sex), model 3: adjusted for age, (sex,) systolic blood pressure and antihypertensive medication use, body mass index, fasting plasma glucose and use of glucose-lowering medication, low-density lipoprotein cholesterol, triglycerides and lipid-lowering medication

SpQRSTa showed poor discriminative ability for cIMT >p75 (AUC: 0.56; 95%CI: 0.55 – 0.58), cIMT >p95 (0.56; 0.53 – 0.58) and cIMT >p99 (0.56; 0.53 – 0.58) as well as for PWV >p75 (0.52; 0.50 – 0.53), PWV >p95 (0.50; 0.49 – 0.52) and PWV >p99 (0.50; 0.49 – 0.52). As presented in Table 2, addition of spQRSTa to the variables age, sex, BMI, systolic blood pressure and smoking did not improve discriminative ability for either cIMT or PWV.

Table 2. Discriminative ability of spQRSTa and risk factors for normal/high cIMT or PWV

	AUC (95% confidence interval)					
	cIMT			PWV		
	p75	p95	p99	p75	p95	p99
spQRSTa	0.56 (0.55 - 0.58)	0.56 (0.53 – 0.58)	0.56 (0.53 – 0.58)	0.52 (0.50 – 0.53)	0.50 (0.49 – 0.52)	0.50 (0.49 – 0.52)
Age, sex, BMI, systolic blood pressure, smoking	0.68 (0.66 – 0.69)	0.67 (0.65 – 0.70)	0.61 (0.56 – 0.66)	0.63 (0.61 – 0.64)	0.57 (0.56 – 0.59)	0.57 (0.56 – 0.59)
Age, sex, BMI, systolic blood pressure, smoking & spQRSTa	0.68 (0.66 – 0.69)	0.67 (0.65 – 0.70)	0.61 (0.56 – 0.66)	0.63 (0.61 – 0.64)	0.57 (0.56 – 0.59)	0.57 (0.56 – 0.59)

Results are presented as area under the receiver operating characteristic curve with 95% confidence interval. Results are based on analyses weighted towards the body mass index distribution of the general population

AUC, area under the curve; BMI, Body Mass Index; p, percentile; cIMT, carotid intima media thickness; PWV, pulse wave velocity; spQRSTa, spatial QRS-T angle cIMT: p75, 0.7 mm; p95, 0.8 mm; p99, 0.9 mm. PWV: p75, 7.2 m/s; p95, 9.1 m/s; p99, 10.3 m/s

DISCUSSION

In this large cohort study with over 6000 ECGs we found the cardiovascular risk factors age, BMI and blood pressure to be associated with a wider spQRSTa. In addition, spQRSTa was wider in participants with impaired fasting glucose, high fasting glucose or T2DM, compared with participants with a normal glucose metabolism. Furthermore, we found associations of greater cIMT and PWV with a wider spQRSTa. As expected, after adjustment for classical cardiovascular risk factors, associations attenuated. Furthermore, adding spQRSTa on top of age, sex, BMI, systolic blood pressure and smoking was not useful in a model used for discriminating between normal and high cIMT or PWV.

Several studies have previously found cardiovascular risk factors, including also blood pressure, LDL-cholesterol, triglycerides, metabolic syndrome score, T2DM and increased fasting plasma glucose to be associated with a wider spQRSTa [1-7]. Moreover, it has been reported that the spQRSTa is on average wider in men then in women, which is confirmed here [25-27]. We also demonstrated a wider spQRSTa in participants with fasting plasma glucose of 6.1-7.0 mmol/l and an even wider spQRSTa in participants with fasting plasma glucose >7.0 mmol/l. In participants with T2DM (history or medication use), the spQRSTa is somewhat narrower compared with participants with fasting plasma glucose >7.0mmol/l, which is most likely due to the high percentage of glucose-lowering medication use in the T2DM subgroup (74%). One possible explanation for the wider spQRSTa found in diabetic individuals, and also already in individuals with impaired fasting glucose, involves the increased sympathetic nervous system activity that can be seen in these individuals and could contribute to the changes in myocardial repolarization [28]. Furthermore, T2DM and pre-diabetes have been associated with premature atherosclerosis, peripheral artery disease and stiffening of the blood vessels. Several mechanisms are involved in diabetic cardiomyopathy, among which interstitial fibrosis, hypertrophy, cardiac autonomic neuropathy, changes in myocardial substrate and energy metabolism, myocardial damage and changes (functional or structural) of the small coronary vessels [29,30].

Several studies have investigated adverse outcomes that are associated with, or can be predicted by a wider or abnormal spQRSTa. After adjustment for several classical cardiovascular risk factors, abnormal or wider spQRSTa was associated with cardiovascular events in women [14], with coronary heart disease events and congestive heart failure in postmenopausal women [11,12], with all-cause mortality (especially sudden cardiac death) in dialysis patients [10], with increased risk of cardiac mortality but not non-fatal cardiac events in an older general population [13], and with all-cause and cardiovascular mortality in US adults without known heart disease [3]. In a large population-based study, abnormal spQRSTa was associated with increased risk of coronary heart disease and total mortality in women, but not in men [15].

Furthermore, in a large clinical population, abnormal spQRSTa was associated with cardiovascular mortality, after adjustment for age and sex, but not for other classical cardiovascular risk factors [6]. Associations of atherosclerosis and arterial stiffness with spQRSTa, which are observed in this present study, have to our knowledge not been demonstrated before. As expected, the observed associations between cIMT and PWV and

a wider spQRSTa in this study attenuated after adjustment for classical cardiovascular risk factors. It is plausible that these risk factors are common causes of both increased cIMT or PWV and a wider spQRSTa, leading to this attenuation of the observed associations after adjustment for these risk factors. Furthermore, the spQRSTa did not show potential added value when added to some simple cardiovascular risk factors in a model used for discriminating between participants with normal and high cIMT or PWV. Although spQRSTa was not able to discriminate between participants with normal or high cIMT or PWV, spQRSTa was shown to be useful in cardiovascular risk stratification in several studies, as described above.

Strenghts and limitations

A strength of this study is the large number of participants with measurement of the spQRSTa in combination with cIMT (n=6278) and PWV (n=2369) that was included. A limitation is that this study consists of cross-sectional analyses, which hampers conclusions on causal mechanisms.

Conclusion

Cardiovascular risk factors are associated with a wider spQRSTa. Furthermore, greater cIMT and PWV were associated with a wider spQRSTa. The spQRSTa was not found to be useful in a model used for discriminating between participants with normal and high cIMT or PWV.

The spQRSTa can be computed from the electrocardiogram, a low-cost and widely used medical tool, especially in the field of cardiology. Several studies have previously found the spQRSTa to be a prognostic factor for cardiovascular disease and mortality [3,6,10-15]. Other mechanisms that could contribute to widening of the spQRSTa should be further elucidated to examine the role of the spQRSTa as marker and predictor of cardiovascular disease.

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REFERENCES

1. de Torbal A, Kors JA, van Herpen G, Meij S, Nelwan S, Simoons ML, et al. The electrical T-axis and the spatial QRS-T angle are independent predictors of long-term mortality in patients admitted with acute ischemic chest pain. Cardiology. 2004;101:199-207.
2. Voulgari C, Tentolouris N, Papadogiannis D, Moyssakis I, Perrea D, Kyriaki D, et al. Increased left ventricular arrhythmogenicity in metabolic syndrome and relationship with myocardial performance, risk factors for atherosclerosis, and low-grade inflammation. Metabolism. 2010;59:159-65.
3. Whang W, Shimbo D, Levitan EB, Newman JD, Rautaharju PM, Davidson KW, et al. Relations between QRS|T angle, cardiac risk factors, and mortality in the third National Health and Nutrition Examination Survey (NHANES III). Am J Cardiol. 2012;109:981-7.
4. Voulgari C, Moyssakis I, Perrea D, Kyriaki D, Katsilambros N, Tentolouris N. The association between the spatial QRS-T angle with cardiac autonomic neuropathy in subjects with Type 2 diabetes mellitus. Diabet Med. 2010;27:1420-9.
5. Atsma F, Bartelink ML, van der Schouw YT, Kors JA, Grobbee DE. Elevated blood pressure and electrocardiographic frontal T axis and spatial QRS-T angle changes in postmenopausal women. J Electrocardiol. 2008;41:360-4.
6. Yamazaki T, Froelicher VF, Myers J, Chun S, Wang P. Spatial QRS-T angle predicts cardiac death in a clinical population. Heart rhythm. 2005;2:73-8.
7. Voulgari C, Tentolouris N, Moyssakis I, Dilaveris P, Gialafos E, Papadogiannis D, et al. Spatial QRS-T angle: association with diabetes and left ventricular performance. Eur J Clin Invest. 2006;36:608-13.
8. Hurst JW. Thoughts about the ventricular gradient and its current clinical use (part II of II). Clin Cardiol. 2005;28:219-24.
9. Macfarlane PW, Edenbrandt L, Pahlm O. 12-Lead vectorcardiography. Butterworth Heinemann. 1995.
10. de Bie MK, Koopman MG, Gaasbeek A, Dekker FW, Maan AC, Swenne CA, et al. Incremental prognostic value of an abnormal baseline spatial QRS-T angle in chronic dialysis patients. Europace. 2013;15:290-6.
11. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic predictors of incident congestive heart failure and all-cause mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006;113:481-9.
12. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006;113:473-80.
13. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J. 2003;24:1357-64.
14. Triola B, Olson MB, Reis SE, Rautaharju P, Merz CN, Kelsey SF, et al. Electrocardiographic predictors of cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. J Am Coll Cardiol. 2005;46:51-6.
15. Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM, Group AR. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). Am J Cardiol. 2007;100:844-9.

16. Jaroszynski A, Czekajska-Chechab E, Drelich-Zbroja A, Zapolski T, Ksiazek A. Spatial QRS-T angle in peritoneal dialysis patients: association with carotid artery atherosclerosis, coronary artery calcification and troponin T. Nephrol Dial Transplant. 2009;24:1003-8.
17. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013;28:513-23.
18. Macfarlane PW, Devine B, Clark E. The University of Glasgow (Uni-G) ECG Analysis Program. Comput Cardiol. 2005:451–4.
19. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.
20. Man SC, Maan AC, van der Wall EE, Schalij MJ, Swenne CA. Beats: an interactive research oriented ECG analysis system. Comput Cardiol. 2010;37:1007-10.
21. Draisma HHM, Swenne CA, van der vooren H, Maan AC, Hooft van Huysduynen B, van der Wall EE, et al. LEADS: an interactive research oriented ECG/VCG analysis system. Comput Cardiol. 2005;32:515-8.
22. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health. 1991;81:1166-73.
23. Lumley T. Analysis of complex survey samples. J Stat Softw. 2004; 9:1-19.
24. Ministerie van VWS. Hoeveel mensen hebben overgewicht? NdMG. 2014.
25. Scherptong RW, Henkens IR, Man SC, Le Cessie S, Vliegen HW, Draisma HH, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. J Electrocardiol. 2008;41:648-55.
26. Rautaharju PM, Zhou SH, Gregg RE, Startt-Selvester RH. Heart rate, gender differences, and presence versus absence of diagnostic ST elevation as determinants of spatial QRS|T angle widening in acute coronary syndrome. Am J Cardiol. 2011;107:1744-50.
27. Smetana P, Batchvarov VN, Hnatkova K, Camm AJ, Malik M. Sex differences in repolarization homogeneity and its circadian pattern. Am J Physiol Heart Physiol. 2002;282:H1889-97.
28. Scherrer U, Sartori C. Insulin as a vascular and sympathoexcitatory hormone: implications for blood pressure regulation, insulin sensitivity, and cardiovascular morbidity. Circulation. 1997;96:4104-13.
29. Boudina S, Abel ED. Diabetic cardiomyopathy, causes and effects. Rev Endocr Metab Disord. 2010;11:31-9.
30. Aneja A, Tang WH, Bansilal S, Garcia MJ, Farkouh ME. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. Am J Med. 2008;121:748-57.

CHAPTER 7

Improvement of electrocardiographic detection of left ventricular hypertrophy by body mass index and spatial QRS-T angle

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ABSTRACT

Background

Left ventricular hypertrophy (LVH) is an important risk factor for adverse cardiovascular outcomes. Improvement of electrocardiographic criteria for LVH is desirable since electrocardiography is widely used. We investigated improvement of electrocardiographic LVH detection by adding measures of adiposity and/or novel electrocardiographic measures.

Methods

We included 1091 participants of the Netherlands Epidemiology of Obesity Study who underwent cardiac magnetic resonance imaging (MRI). Performance of Sokolow-Lyon and Cornell voltage and product criteria was assessed. Stepwise regression analyses was performed with each conventional electrocardiographic criterion and age, sex, body mass index (BMI), waist circumference and waist:hip ratio (p-entry <0.05, p-removal >0.10). T-wave abnormalities or the spatial QRS-T angle (SA) were added to the improved models.

Results

The study population had a mean (SD) age of 56 (6)years, BMI of 26.1 (4.0) kg/m^2 and 46% were men. MRI-LVH was present in 11% of participants. C-statistic for Sokolow-Lyon voltage was 0.60, R^2 0.03 and sensitivity at 90% specificity was 17%, for Sokolow-Lyon product 0.63, 0.04 and 23%, for Cornell voltage 0.65, 0.03 and 27% and for Cornell product 0.67, 0.04 and 26%. Best performing models with Sokolow-Lyon criteria were obtained by addition of both BMI and SA (voltage: c-statistic 0.75, R^2 0.12, sensitivity of 41% at 90% specificity; product: 0.76, 0.13, 43%) and for models with Cornell criteria by adding BMI (voltage: 0.70, 0.07, 35%; product: 0.72, 0.07, 36%).

Conclusions

Electrocardiographic detection of LVH improved by adding BMI and SA to a model with conventional electrocardiographic criteria. This requires little extra effort and application in clinical practice is feasible. Results should be replicated in high-risk populations.

INTRODUCTION

Left ventricular hypertrophy (LVH) is an important risk factor for cardiovascular events and cardiovascular death [1,2]. Several electrocardiographic criteria for the diagnosis of LVH exist, e.g. Sokolow-Lyon voltage and Cornell voltage criterion. However these criteria show limited performance compared with diagnosis of LVH by echocardiography or (the 'gold standard') cardiac magnetic resonance imaging (MRI). With acceptable specificities, sensitivities are often low (7-40% for Sokolow-Lyon voltage and 2-19% for Cornell voltage criterion) [3]. Nevertheless, electrocardiograms (ECG) are more easily obtainable and cost-effective compared with echocardiography or cardiac MRI, and for those reasons are more often used in current clinical practice. Therefore, improvement of the electrocardiographic diagnosis of LVH is desired.

The performance of electrocardiographic criteria for the diagnosis of LVH can be influenced by body fat. Obesity is often accompanied by systemic hypertension and is associated with a higher prevalence of LVH, but also, adipose tissue can attenuate electrocardiographic voltages, which interferes with LVH detection by electrocardiographic criteria [4, 5]. To take measures of body fat together with conventional electrocardiographic criteria into the diagnostic model for LVH has previously been proposed in the literature as a method that might lead to improved electrocardiographic LVH detection [5-8]. Several studies investigated the addition of BMI and showed improved performance [5-8]. However, to our knowledge, there are no studies investigating the addition of other measures of body fat and body fat distribution to the conventional electrocardiographic criteria.

Furthermore, LVH is associated with alterations in ventricular repolarization and depolarization through several mechanisms such as an increase in collagen interstitial matrix or changes in ionic channels [9-11]. These changes in ventricular depolarization and repolarization can be reflected in T-wave abnormalities and the spatial QRS-T angle [12], which can both be determined from the ECG. Therefore these measures might also be useful in the electrocardiographic diagnosis of LVH. It was previously shown that a combination of body surface area and spatial QRS-T angle can improve electrocardiographic diagnosis of LVH [13].

This study aimed to investigate whether addition of measures of body fat and body fat distribution and additional T-wave abnormalities or spatial QRS-T angle to conventional electrocardiographic criteria of LVH could improve the electrocardiographic detection of LVH.

METHODS

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort study including 6671 individuals. Men and women aged between 45 and 65 years with a BMI of 27 kg/m^2 or higher living in the area of greater 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. Of the participants without contra-indications for MRI (most notably metallic devices, claustrophobia or a body circumference of more than 1.70 m) a random subsample of approximately 20% of participants underwent cardiac MRI. Individuals completed a questionnaire with demographic, lifestyle, and clinical information. At the study centre in the Leiden University Medical Centre (LUMC) all individuals underwent an extensive physical examination, including anthropometry, blood sampling (after an overnight fast) and electrocardiography. The present analysis is a cross-sectional analysis using the baseline measurements of the NEO study. We excluded participants in whom no cardiac MRI was performed or measurement of left ventricular mass (LVM) was missing, participants with abnormalities that could interfere with the electrocardiographic detection of LVH or the assessment of the spatial QRS-T angle, namely individuals with complete bundle branch block, ventricular pre-excitation (Wolff-Parkinson-White syndrome), previous myocardial infarction or a paced rhythm, and also individuals with missing values of the spatial QRS-T angle. Further details of the study design and population have been described in detail elsewhere [14]. The Medical Ethical Committee of the Leiden University Medical Center approved the design of the study and all individuals gave their written informed consent.

Data collection

Ethnicity was self-identified in eight categories and grouped into white and other. Body height and weight were measured without shoes and 1 kg was subtracted from the weight to correct for clothing. Waist circumference was measured with a horizontally placed flexible tape in the middle of the distance between the lowest rib and the iliac crest. Hip circumference was measured at the maximum circumference of the buttocks. Brachial blood pressure was measured in a seated position on the right arm using a validated automatic oscillometric device (OMRON, Model M10-IT, Omron Health Care Inc, IL, USA). Blood pressure was measured three times with 5 minutes rest between consecutive measurements. The mean systolic and diastolic blood pressure was calculated. Blood samples were drawn after an overnight fast of 10 hours. Fasting glucose was measured with the enzymatic colorimetric method (Roche Modular Analytics P800, Roche Diagnostics Mannheim, Germany).

Electrocardiography

After a resting period of at least 10 minutes, 12-lead ECGs were obtained using a Mortara Eli-350 (Mortara Instrument Inc., Milwaukee, WI, USA). The raw data were extracted and transferred to the University of Glasgow ECG core lab where ECGs were automatically processed and Minnesota codes were assigned using the University of Glasgow ECG analysis program [15]. We investigated four conventional electrocardiographic criteria for LVH (continuous variables): two widely used voltage index electrocardiographic criteria, namely Sokolow-Lyon voltage and Cornell voltage, and two voltage-duration product criteria, namely Sokolow-Lyon product, and Cornell product [16-20]. Sokolow-Lyon voltage was defined as |SV1|+RV5/6 and Sokolow-Lyon product as Sokolow-Lyon voltage x QRS duration. Cornell voltage was defined as RaVL+|SV3| with 600 µV added for women and Cornell product was defined as Cornell Voltage x QRS duration. T-wave abnormalities were defined as Minnesota Codes 5-1 or 5-2.

Standard 10-second ECGs were each stored in an 8-lead (I, II, II, V1-V6), 5000 sample comma-separated-value file. The Kors matrix was used to calculate vector cardiograms from the eight independent ECG leads [21]. ECGs and vector cardiograms were analyzed using the automatic MATLAB-based (The MathWorks, Natick, MA) program BEATS and the semiautomatic program LEADS [22,23]. BEATS was used to detect the timings of all QRS complexes and calculated R-R intervals (ms). The QRS and T integral vectors were approximated by calculating the numerical sum of x-y-z deflections (amplitudes of positive deflections are added and those of negative deflections subtracted). The spatial QRS-T angle was defined as the angle (°) between the integral QRS vector and the integral T vector.

Magnetic resonance imaging

In 1150 participants LVM was assessed using cardiac magnetic resonance imaging. The heart was imaged in the short-axis orientation by using ECG gated breath-hold balanced steady-state free precession imaging. Data were analysed using in-house software (MASS and FLOW; LUMC, Leiden, the Netherlands).

LVM was indexed by height to obtain left ventricular mass index (LVMI). LVM was not indexed by body surface area to prevent underestimation of the prevalence of LVH in the NEO study population, which has a high prevalence of overweight and obese individuals [24]. Cut-offs for LVH were based on the sex-specific upper limits of normality (95th percentile) from a subgroup of 252 healthy individuals from the NEO study, with a BMI<30 kg/m^2, normal blood pressure (<135/<85 mmHg and no use of antihypertensive medication), no history of cardiovascular disease and normal glucose metabolism (no self-reported diabetes mellitus I or II or medication and fasting plasma glucose <7 mmol/L). LVH was defined as LVMI > 78.7 g/m in men and LVMI > 60.0 g/m in women.

Statistical analysis

Adjustments for the oversampling of individuals with BMI ≥ 27 kg/m^2 in the NEO study were made to correctly represent baseline associations in the general population [25]. This was done by weighting individuals towards the BMI distribution of participants from the Leiderdorp municipality, whose BMI distribution was similar to the BMI distribution of the general Dutch population [26]. Baseline characteristics are presented as mean (SD), median (IQR) or as percentage (%).

First, univariate discriminative performance for LVH of the conventional electrocardiographic criteria, namely Sokolow-Lyon voltage, Sokolow-Lyon product, Cornell voltage and Cornell product was assessed using the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. The AUC reflects how well individuals are classified as having LVH or no LVH. Also, sensitivities of the conventional electrocardiographic criteria were determined at a specificity of 90%, since especially specificities of 90-100% are clinically relevant for detection of LVH. Second, univariate discriminative performance for LVH of age, sex, BMI, waist circumference and waist:hip ratio was assessed with the AUC. Then, stepwise logistic regression analysis with an entry criterion of p<0.05 and removal criterion of p>0.10 was performed with LVH as dependent variable and each conventional electrocardiographic

criterion separately with addition of the variables age, sex, BMI, waist circumference and waist:hip ratio as independent variables. AUC, R^2 and sensitivity at 90% specificity of the selected models were assessed. Univariate discriminative performance for LVH of T-wave abnormalities (dichotomous) and the spatial QRS-T angle was also assessed using the AUC. Finally, for each conventional electrocardiographic criterion separately, best performing models were determined, consisting of a combination of the best performing measure of body fat and the best of T-wave abnormalities and spatial QRS-T angle. AUC, R^2, sensitivities at a specificity of 90% and calibration plots were reported for the new models for LVH detection. Furthermore, the internal validity of the estimated AUC values was assessed using bootstrapping. Data were analysed using STATA (Statacorp, College Station, Texas, USA), version 14.

Table 1. Characteristics of 1091 participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity study

Age, years	56 (6)
Sex, men, %	46
Ethnicity, white, %	96
Physical activity (MET-hour/week)	16 (32-53)
Systolic blood pressure, mmHg	131.5 (18.2)
Diastolic blood pressure, mmHg	84.1 (10.8)
Use of antihypertensive therapy, %	22
History of cardiovascular disease, %	4
BMI, kg/m^2	26.1 (4.0)
Waist circumference, cm	91.7 (12.6)
WHR	0.9 (0.1)
LVM, g	96.7 (25.7)
LVM index, g/m	55.5 (12.9)
LVH (MRI based), %	11
Sokolow-Lyon Voltage, µV	1981 (625)
Sokolow-Lyon Product, µV.ms	182377 (63038)
Cornell Voltage, µV	1366 (437)
Cornell Product, µV.ms	97570 (47978)
Spatial QRS-T angle, °	52.8 (26.6)
T-wave abnormalities, %	2

Data are presented as mean (SD), median (interquartile range), or percentages.
Results were based on analyses weighted towards the BMI distribution of the general population (n=1091). History of cardiovascular disease: angina, congestive heart failure, stroke, or peripheral vascular disease. BMI, body mass index; MET, metabolic equivalent of task; LVH, left ventricular hypertrophy; LVM, left ventricular mass; MRI, magnetic resonance imaging; WHR, waist:hip ratio

RESULTS

Cardiac magnetic resonance imaging was performed in 1278 participants. Participants in whom measurement of LVM was missing (n=128), in addition to participants with left or right bundle branch block (n=21), history of myocardial infarction (n=14), Wolff-Parkinson-White syndrome (n=1) or missing spatial QRS-T angle (n=23) were excluded. Baseline characteristics of the 1091 individuals included in the study are presented in Table 1. The study population had a mean (SD) age of 56 (6) years and 46% were men. Mean (SD) blood pressure was 131.5 (18.2)/84.1 (10.8) mmHg and 22% of the study population was taking antihypertensive medication. According to the MRI-based sex-specific cut-offs, 11% of this study population was defined as having LVH.

Univariate discriminative performance of the conventional electocardiographic criteria alone was poor. AUC for Sokolow-Lyon voltage was 0.60 (95%CI: 0.55 , 0.65) and R^2 0.03, for Sokolow-Lyon product 0.63 (0.59 , 0.68) and 0.04, for Cornell voltage 0.65 (0.60 , 0.70) and 0.03 and for Cornell product 0.67 (0.62 , 0.71) and 0.04. Furthermore, at a specificity of 90%, Sokolow-Lyon voltage showed a sensitivity of 17%, Sokolow-Lyon product a sensitivity of 23%, Cornell voltage a sensitivity of 27% and Cornell product a sensitivity of 26%. ROC curves for the conventional electrocardiographic criteria are displayed in Figure 1a.

Univariate discriminative performance of age, sex, BMI, waist circumference and waist:hip ratio was also estimated with the AUC. BMI (0.67, 95%CI: 0.63 , 0.72), waist circumference (0.66; 0.61 , 0.70) and waist:hip ratio (0.57; 0.52 , 0.61) showed discriminative power for LVH, whereas age (0.48; 0.44 , 0.53) and sex (0.52; 0.48 , 0.56) did not. ROC curves for age, sex, BMI, waist circumference and waist:hip ratio are displayed in Figure 1b.

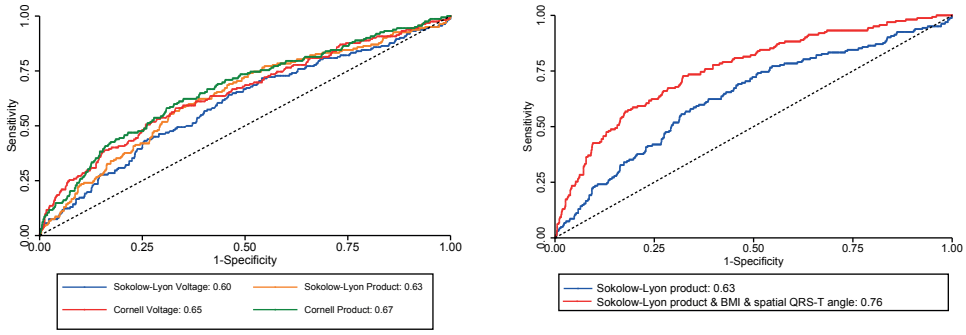

Figure 1. Receiver Operating Characteristic curves and area under the curve values of electrocardiographic criteria
(1a) and age, sex, body mass index, waist circumference and waist:hip ratio (1b) for detection of LVH, in 1091 participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity study. Results were based on analyses weighted towards the BMI distribution of the general population. BMI, Body Mass Index; WHR, waist:hip ratio

Using stepwise regression analyses with the variables age, sex, BMI, waist circumference and waist:hip ratio, models for each conventional electrocardiographic criterion and additionally BMI were selected. Addition of BMI to models with Sokolow-Lyon voltage, improved the AUC to 0.72 ($p<0.01$) and AUC was improved to 0.74 for Sokolow-Lyon product ($p<0.01$), 0.70 for Cornell voltage ($p=0.01$) and 0.72 for Cornell product ($p=0.01$). The addition of BMI also led to improvements in R^2 and sensitivity at 90% specificity, as shown in Table 2.

Table 2. Performances of conventional electrocardiographic criteria for detection of left ventricular hypertrophy alone and with addition of body mass index, in 1091 participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity study

	AUC	R^2	Sensitivity at 90% specificity
Sokolow-Lyon voltage (Sok V)	0.60 (0.55 , 0.65)	0.03	17%
Sok V & BMI	0.72 (0.68 , 0.76)	0.10	31%
Sokolow-Lyon product (Sok P)	0.63 (0.59 , 0.68)	0.04	23%
Sok P & BMI	0.74 (0.70 , 0.78)	0.11	36%
Cornell voltage (Cor V)	0.65 (0.60 , 0.70)	0.03	27%
Cor V & BMI	0.70 (0.65 , 0.74)	0.07	35%
Cornell product (Cor P)	0.67 (0.62 , 0.71)	0.04	26%
Cor P & BMI	0.72 (0.67 , 0.76)	0.07	36%

Results were based on analyses weighted towards the BMI distribution of the general population.
AUC, area under the curve; BMI, body mass index

The addition of waist circumference to models with the conventional electrocardiographic criteria also led to improvements in R^2 and sensitivity at 90% specificity, as shown in supplementary Table 1. Addition of waist circumference led to smaller improvement of the models than the addition of BMI did.

Presence of T-wave abnormalities (dichotomous) had poor discriminative performance for LVH with AUC 0.51 and this was 0.61 for spatial QRS-T angle (ROC curves shown in supplementary Figure 1). When T-wave abnormalities were added to models with each conventional electrocardiographic criteria in combination with BMI, AUC did not improve (results not shown).

Addition of spatial QRS-T angle to the models with each conventional electrocardiographic criterion and BMI did lead to improved performance, as is presented in Table 3. Models with the conventional electrocardiographic criteria and additionally BMI and for Sokolow-Lyon voltage and product also additionally spatial QRS-T angle showed the best performance. ROC curves for these models, compared with models with each electrocardiographic criterion alone, are presented in Figure 2. The combination of Sokolow-Lyon voltage, BMI

and spatial QRS-T angle showed an AUC of 0.75, R^2 of 0.12 and a sensitivity of 41% at a matched specificity of 90%. This was 0.76, 0.13 and 43% for the combination of Sokolow-Lyon product, BMI and spatial QRS-T angle, 0.70, 0.07 and 35% for the combination of Cornell voltage and BMI and 0.72, 0.07 and 36% for the combination of Cornell product and BMI. For these four models, calibration plots are presented in Supplementary Figure 2. Furthermore, bootstrapping showed good internal validity for the estimated AUC values. In conclusion, the best performance in the detection of LVH was reached by a combination of Sokolow-Lyon product, BMI and spatial QRS-T angle.

Table 3. Performances of conventional electrocardiographic criteria for detection of left ventricular hypertrophy with addition of BMI alone and both BMI and spatial QRS-T angle, in 1091 participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity study

	AUC	R^2	Sensitivity at 90% specificity
Sokolow-Lyon voltage (Sok V) & BMI	0.72 (0.68 , 0.76)	0.10	31%
Sok V & BMI & spatial QRS-T angle	0.75 (0.70 , 0.79)	0.12	41%
Sokolow-Lyon product (Sok P) & BMI	0.74 (0.70 , 0.78)	0.11	36%
Sok P & BMI & spatial QRS-T angle	0.76 (0.71 , 0.80)	0.13	43%
Cornell voltage (Cor V) & BMI	0.70 (0.65 , 0.74)	0.07	35%
Cor V & BMI & spatial QRS-T angle	0.70 (0.65 , 0.75)	0.07	35%
Cornell product (Cor P) & BMI	0.72 (0.67 , 0.76)	0.07	36%
Cor P & BMI & spatial QRS-T angle	0.71 (0.67 , 0.76)	0.08	39%

Results were based on analyses weighted towards the BMI distribution of the general population.
AUC, area under the curve; BMI, body mass index

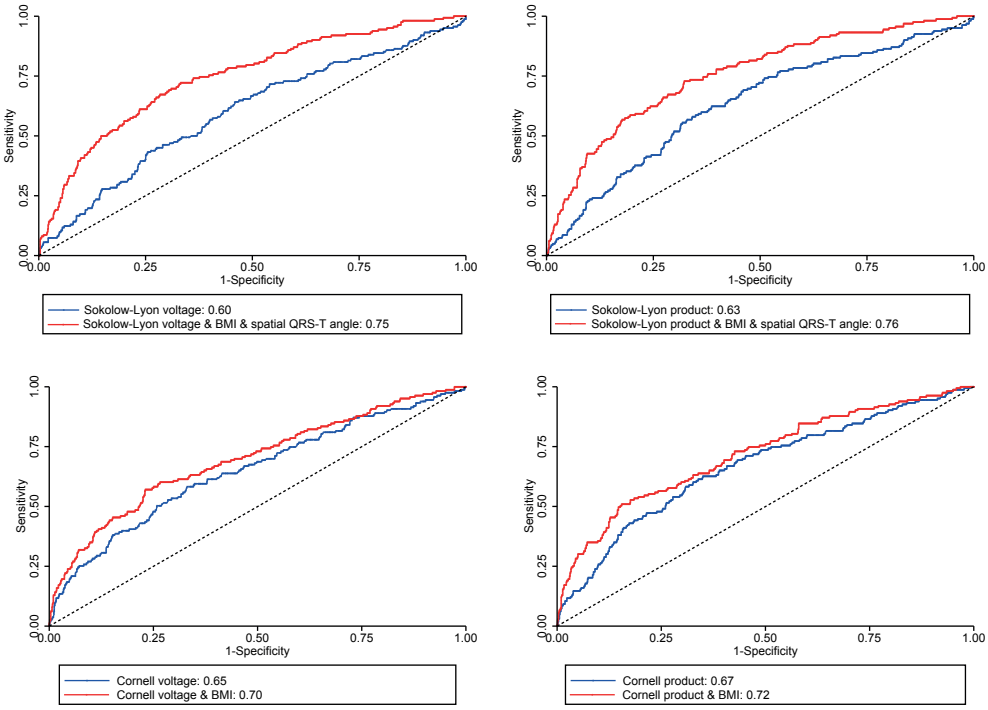

Figure 2. Receiver Operating Characteristic curves and area under the curve values of the conventional electrocardiographic criteria alone and with addition body mass index and additionally spatial QRS-T angle for Sokolow-Lyon voltage and product for detection of left ventricular hypertrophy, in 1091 participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity study. Results were based on analyses weighted towards the BMI distribution of the general population. BMI, body mass index

DISCUSSION

In this population of middle-aged men and women, in whom cardiac MRI was performed, adding BMI (which is easily determinable) to conventional electrocardiographic criteria, more so than waist circumference or waist:hip ratio, improved performance in detection of LVH. Additionally adding the spatial QRS-T angle to the models with Sokolow-Lyon voltage and product and BMI improved performance even further. For example, AUC for detection of LVH of Sokolow-Lyon product was 0.63 and sensitivity at a specificity of 90% was 23%, and with addition of BMI and spatial QRS-T angle this improved to AUC 0.76 and 43%.

The poor performance of conventional electocardiographic criteria for LVH detection has previously been described [3]. A systematic review showed that in primary care settings, sensitivity of Sokolow-Lyon voltage criteria ranged from 8-40% at specificities 53-100% and sensitivity of Cornell voltage criteria ranged from 2-19% at specificities 89-100% [3]. In individuals with systemic hypertension, the combination of Cornell voltage with BMI improved the performance in LVH detection [6]. In a population-based study (n=3351), adding

both BMI and age to Cornell product improved its performance [8] and in another study adding BMI to Sokolow-Lyon voltage or Cornell voltage improved their performance [5]. To our knowledge, few studies investigated addition of spatial QRS-T angle to electrocardiographic LVH criteria [13]. In 196 individuals a combination of body surface area and spatial QRS-T angle yielded the best diagnostic accuracy for LVH (using echocardiography as reference standard), superior to that of conventional electrocardiographic criteria [13]. In our study, a combination of BMI and spatial QRS-T angle alone (without other electrocardiographic criteria) would yield an AUC of 0.69, which is higher than the AUC of the conventional electrocardiographic criteria alone, but, however not higher than the conventional electrocardiographic criteria combined with BMI and spatial QRS-T angle.

Interpretation and mechanisms

LVH is a pathological remodelling of the left ventricle, often in response to increased afterload. Presence of increased afterload is commonly seen with systemic hypertension, increased peripheral resistance and increased arterial stiffness, which are prevailing in obese individuals [27]. Next to the known association of obesity with an increased risk of LVH, several studies showed that electrocardiographic criteria for LVH have very limited performance, especially in obese individuals [28,29]. Also in this present study, discriminative performance of the conventional electrocardiographic criteria is poor, especially of the Sokolow-Lyon criteria (AUC Sokolow-Lyon voltage 0.60, Sokolow-Lyon product 0.63). Probably, precordial electrocardiographic voltages (affecting Sokolow-Lyon voltage and product more than Cornell voltage and product) are reduced due to the presence of increased epicardial fat mass and a large chest wall, which corresponds to the findings in this present study. Before addition of BMI to the conventional electrocardiographic criteria, Sokolow-Lyon voltage and product performed worse than Cornell voltage and product, and after adjustment for BMI, performances of Sokolow-Lyon and Cornell criteria were similar. This may partly be explained by the fact that the Sokolow-Lyon criteria depend more on precordial voltages than Cornell criteria do.

Hypertrophy of the left ventricle is often accompanied by electrophysiological changes and repolarization inhomogeneities [30]. In the hypertrophic heart, action potential duration is prolonged because of delayed conduction and also several other mechanisms are at play, among which are alterations in ionic channels and changes in ventricular repolarization induced by an increase in collagen interstitial matrix [9-11, 31, 32]. These changes can be reflected in T-wave abnormalities or widening of the spatial QRS-T angle, as described in literature [33-35]. Computation of the spatial QRS-T angle from the ECG has become easier and therefore taking into account the spatial QRS-T angle in detecting LVH, which is shown valuable in this study, could possibly be translated into clinical practice.

Strengths and limitations

This study has several important strengths. Firstly, LVH was determined by 'the gold standard' MRI in a large number of individuals (n=1091), in whom also electrocardiographic LVH criteria, spatial QRS-T angle and T-wave abnormalities were available. Also, we were able to assess addition of several anthropometric measures, whereas other studies could

only investigate addition of BMI. Several limitations apply to this study. First, since our study was performed in a population-based cohort of mostly white, middle-aged individuals (45-65 years), extrapolation to other populations with different ethnic backgrounds, age ranges or patient populations should be done with caution. Furthermore, in this study we chose to focus on four widely used electrocardiographic criteria of LVH. However, more electrocardiographic criteria for LVH diagnosis exist, which were not included in this study, since they are less often used in clinical practice [36]. Finally, the approach requires to be validated in relevant patient populations.

Conclusion

ECGs are easily obtainable, low-cost and widely used in clinical practice, and therefore improvements in electrocardiographic detection of LVH, which is strongly associated with adverse cardiovascular outcomes, is very relevant. This study shows possible improvement of electrocardiographic LVH criteria by addition of BMI and the spatial QRS-T angle, which could be useful in clinical practice. Results provided by this study should first be replicated in different patient populations or more high-risk populations.

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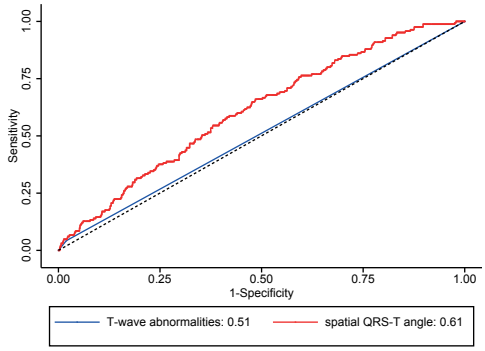
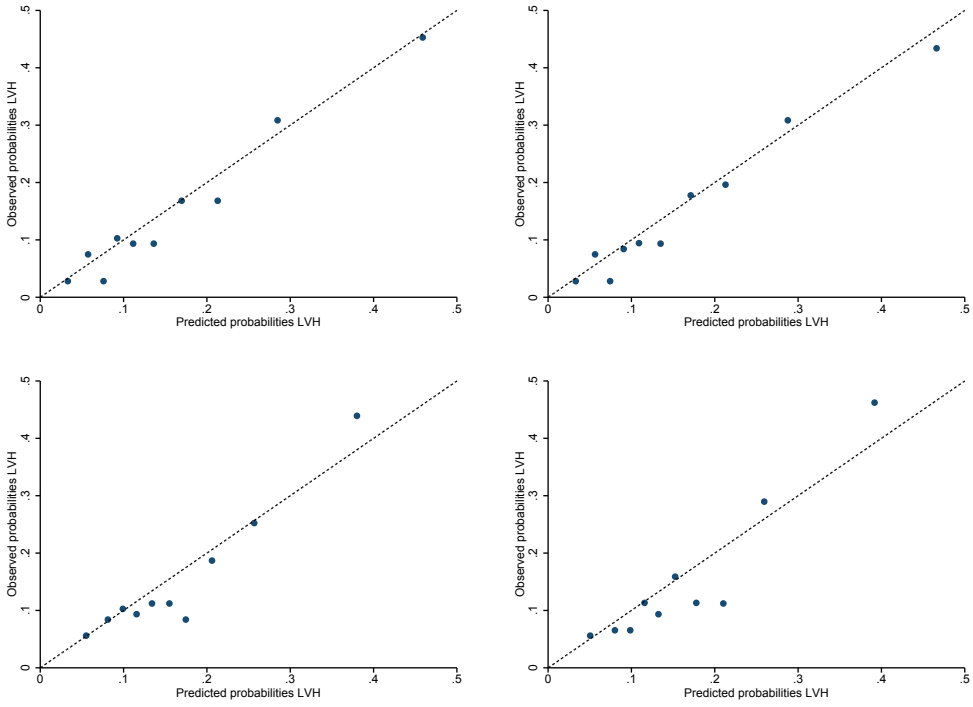


Supplementary Figure 1. Receiver Operating Characteristic curves and area under the curve values of T-wave abnormalities and spatial QRS-T angle for detection of left ventricular hypertrophy, in 1091 participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity study
Results were based on analyses weighted towards the BMI distribution of the general population.
BMI, body mass index



Supplementary Figure 2. Calibration plots for detection of left ventricular hypertrophy of the model of Sokolow-Lyon voltage, body mass index and spatial QRS-T angle (2a), Sokolow-Lyon product, body mass index and spatial QRS-T angle (2b), Cornell voltage and body mass index (2c) and Cornell product and body mass index (2d), in 1091 participants aged 45 to 65 years from the Netherlands Epidemiology of Obesity study

REFERENCES

1. Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram. Prevalence, incidence, and mortality in the Framingham study. Ann Intern Med. 1969;71:89-105.
2. Hawkins NM, Wang D, McMurray JJ, Pfeffer MA, Swedberg K, Granger CB, et al. Prevalence and prognostic implications of electrocardiographic left ventricular hypertrophy in heart failure: evidence from the CHARM programme. Heart. 2007;93:59-64.
3. Pewsner D, Juni P, Egger M, Battaglia M, Sundstrom J, Bachmann LM. Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review. BMJ. 2007;335:711.
4. Masui A, Tsuji H, Tamura K, Tarumi N, Sugiura T, Iwasaka T, et al. Effect of body characteristics on the variables of signal-averaged electrocardiograms in healthy subjects. Chest. 1994;105:1357-9.
5. Cuspidi C, Facchetti R, Bombelli M, Sala C, Tadic M, Grassi G, et al. Does QRS Voltage Correction by Body Mass Index Improve the Accuracy of Electrocardiography in Detecting Left Ventricular Hypertrophy and Predicting Cardiovascular Events in a General Population? J Clin Hypertens. 2016;18:415-21.
6. Angeli F, Verdecchia P, Iacobellis G, Reboldi G. Usefulness of QRS voltage correction by body mass index to improve electrocardiographic detection of left ventricular hypertrophy in patients with systemic hypertension. Am J Cardiol. 2014;114:427-32.
7. Robinson C, Woodiwiss AJ, Libhaber CD, Norton GR. Novel Approach to the Detection of Left Ventricular Hypertrophy Using Body Mass Index-Corrected Electrocardiographic Voltage Criteria in a Group of African Ancestry. Clin Cardiol. 2016;39:524-30.
8. Norman JE Jr., Levy D. Adjustment of ECG left ventricular hypertrophy criteria for body mass index and age improves classification accuracy. The effects of hypertension and obesity. J Electrocardiol. 1996;29 Suppl:241-7.
9. Kleiman RB, Houser SR. Outward currents in normal and hypertrophied feline ventricular myocytes. Am J Physiol. 1989;256:H1450-61.
10. Xu X, Rials SJ, Wu Y, Salata JJ, Liu T, Bharucha DB, et al. Left ventricular hypertrophy decreases slowly but not rapidly activating delayed rectifier potassium currents of epicardial and endocardial myocytes in rabbits. Circulation. 2001;103:1585-90.
11. Pye MP, Cobbe SM. Mechanisms of ventricular arrhythmias in cardiac failure and hypertrophy. Cardiovasc Res. 1992;26:740-50.
12. Draisma HH, Schalij MJ, van der Wall EE, Swenne CA. Elucidation of the spatial ventricular gradient and its link with dispersion of repolarization. Heart rhythm. 2006;3:1092-9.
13. Man S, Rahmattulla C, Maan AC, Holman E, Bax JJ, van der Wall EE, et al. Role of the vectorcardiogram-derived spatial QRS-T angle in diagnosing left ventricular hypertrophy. J Electrocardiol. 2012;45:154-60.
14. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013;28:513-23.
15. Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S. The electrocardiogram in opulation studies. A classification system. Circulation. 1960;21:1160-75.
16. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. Am Heart J. 1949;37:161-86.

17. Casale PN, Devereux RB, Kligfield P, Eisenberg RR, Miller DH, Chaudhary BS, et al. Electrocardiographic detection of left ventricular hypertrophy: development and prospective validation of improved criteria. J Am Coll Cardiol. 1985;6:572-80.
18. Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. Circulation. 1987;75:565-72.
19. Molloy TJ, Okin PM, Devereux RB, Kligfield P. Electrocardiographic detection of left ventricular hypertrophy by the simple QRS voltage-duration product. J Am Coll Cardiol. 1992;20:1180-6.
20. Okin PM, Roman MJ, Devereux RB, Kligfield P. Electrocardiographic identification of increased left ventricular mass by simple voltage-duration products. J Am Coll Cardiol. 1995;25:417-23.
21. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.
22. Man SC, Maan AC, van der Wall EE, Schalij MJ, Swenne CA. Beats: an interactive research oriented ECG analysis system. Comput Cardiol. 2010;37:1007-10.
23. Draisma HHM, Swenne CA, van der Vooren H, Maan AC, Hooft van Huysduynen B, van der Wall EE, et al. LEADS: an interactive research oriented ECG/VCG analysis system. Comput Cardiol. 2005;32:515-8.
24. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440-63.
25. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health. 1991;81:1166-73.
26. Lumley T. Analysis of complex survey samples. J Stat Soft. 2004;9:8.
27. Sutton-Tyrrell K, Newman A, Simonsick EM, Havlik R, Pahor M, Lakatta E, et al. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging, and body composition. Hypertension. 2001;38:429-33.
28. Fraley MA, Birchem JA, Senkottaiyan N, Alpert MA. Obesity and the electrocardiogram. Obes Rev. 2005;6:275-81.
29. Cuspidi C, Rescaldani M, Sala C, Grassi G. Left-ventricular hypertrophy and obesity: a systematic review and meta-analysis of echocardiographic studies. J Hypertens. 2014;32:16-25.
30. Hansen DE. Mechanoelectrical feedback effects of altering preload, afterload, and ventricular shortening. Am J Physiol. 1993;264:H423-32.
31. Winterton SJ, Turner MA, O'Gorman DJ, Flores NA, Sheridan DJ. Hypertrophy causes delayed conduction in human and guinea pig myocardium: accentuation during ischaemic perfusion. Cardiovasc Res. 1994;28:47-54.
32. McIntyre H, Fry CH. Abnormal action potential conduction in isolated human hypertrophied left ventricular myocardium. J Cardiovasc Electrophysiol. 1997;8:887-94.
33. Ishizawa K, Ishizawa K, Motomura M, Konishi T, Wakabayashi A. High reliability rates of spatial pattern analysis by vectorcardiogram in assessing the severity of eccentric left ventricular hypertrophy. Am Heart J. 1976;91:50-7.
34. Dilaveris P, Gialafos E, Pantazis A, Synetos A, Triposkiadis F, Gialafos J. The spatial QRS-T angle as a marker of ventricular repolarisation in hypertension. J Hum Hypertens. 2001;15:63-70.

35. Oikarinen L, Vaananen H, Dabek J, Kaartinen M, Hanninen H, Katila T, et al. Relation of twelve-lead electrocardiographic T-wave morphology descriptors to left ventricular mass. Am J Cardiol. 2002;90:1032-5.
36. Morrison I, Clark E, Macfarlane PW. Evaluation of the electrocardiographic criteria for left ventricular hypertrophy. Anadolu Kardiyol Derg. 2007;7 Suppl 1:159-63.

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.

REFERENCES

1. Bjorntorp P. Adipose tissue distribution and function. Int J Obes. 1991;15 Suppl 2:67-81.
2. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev. 2010;11:11-8.
3. Despres JP. Is visceral obesity the cause of the metabolic syndrome? Ann Med. 2006;38:52-63.
4. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007;116:39-48.
5. Grundy SM. Metabolic syndrome scientific statement by the American Heart Association and the National Heart, Lung, and Blood Institute. Arterioscler Thromb Vasc Biol. 2005;25:2243-4.
6. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med. 2006;119:812-9.
7. Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. Obesity. 2006;14 Suppl 1:16S-9S.
8. Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, et al. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. Am J Epidemiol. 1999;149:853-62.
9. Dhingra R, Pencina MJ, Wang TJ, Nam BH, Benjamin EJ, Levy D, et al. Electrocardiographic QRS duration and the risk of congestive heart failure: the Framingham Heart Study. Hypertension. 2006;47:861-7.
10. Rabkin SW, Mathewson FA, Tate RB. The relationship of marked left axis deviation to the risk of ischemic heart disease. Int J Cardiol. 1981;1:169-78.
11. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardiol. 1993;72:23B-5B.
12. Magnani JW, Johnson VM, Sullivan LM, Gorodeski EZ, Schnabel RB, Lubitz SA, et al. P wave duration and risk of longitudinal atrial fibrillation in persons >/= 60 years old (from the Framingham Heart Study). Am J Cardiol. 2011;107:917-21 e1.
13. Rautaharju PM, Nelson JC, Kronmal RA, Zhang ZM, Robbins J, Gottdiener JS, et al. Usefulness of T-axis deviation as an independent risk indicator for incident cardiac events in older men and women free from coronary heart disease (the Cardiovascular Health Study). Am J Cardiol. 2001;88:118-23.
14. Li Y, Shah AJ, Soliman EZ. Effect of electrocardiographic P-wave axis on mortality. Am J Cardiol. 2014;113:372-6.
15. Higashiyama A, Hozawa A, Murakami Y, Okamura T, Watanabe M, Nakamura Y, et al. Prognostic value of q wave for cardiovascular death in a 19-year prospective study of the Japanese general population. J Atheroscler Thromb. 2009;16:40-50.
16. Kwong RY, Sattar H, Wu H, Vorobiof G, Gandla V, Steel K, et al. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. Circulation. 2008;118:1011-20.
17. de Torbal A, Kors JA, van Herpen G, Meij S, Nelwan S, Simoons ML, et al. The electrical T-axis and the spatial QRS-T angle are independent predictors of long-term mortality in patients admitted with acute ischemic chest pain. Cardiology. 2004;101:199-207.

18. Voulgari C, Tentolouris N, Papadogiannis D, Moyssakis I, Perrea D, Kyriaki D, et al. Increased left ventricular arrhythmogenicity in metabolic syndrome and relationship with myocardial performance, risk factors for atherosclerosis, and low-grade inflammation. Metabolism. 2010;59:159-65.
19. Whang W, Shimbo D, Levitan EB, Newman JD, Rautaharju PM, Davidson KW, et al. Relations between QRS|T angle, cardiac risk factors, and mortality in the third National Health and Nutrition Examination Survey (NHANES III). Am J Cardiol. 2012;109:981-7.
20. Voulgari C, Moyssakis I, Perrea D, Kyriaki D, Katsilambros N, Tentolouris N. The association between the spatial QRS-T angle with cardiac autonomic neuropathy in subjects with Type 2 diabetes mellitus. Diabet Med. 2010;27:1420-9.
21. Atsma F, Bartelink ML, van der Schouw YT, Kors JA, Grobbee DE. Elevated blood pressure and electrocardiographic frontal T axis and spatial QRS-T angle changes in postmenopausal women. J Electrocardiol. 2008;41:360-4.
22. Yamazaki T, Froelicher VF, Myers J, Chun S, Wang P. Spatial QRS-T angle predicts cardiac death in a clinical population. Heart rhythm. 2005;2:73-8.
23. Voulgari C, Tentolouris N, Moyssakis I, Dilaveris P, Gialafos E, Papadogiannis D, et al. Spatial QRS-T angle: association with diabetes and left ventricular performance. Eur J Clin Invest. 2006;36:608-13.
24. Godsk P, Jensen JS, Abildstrom SZ, Appleyard M, Pedersen S, Mogelvang R. Prognostic significance of electrocardiographic Q-waves in a low-risk population. Europace. 2012;14:1012-7.
25. Li Y, Dawood FZ, Chen H, Jain A, Walsh JA 3rd, Alonso A, et al. Minor isolated Q waves and cardiovascular events in the MESA study. Am J Med. 2013;126:450 e9- e16.
26. de Bie MK, Koopman MG, Gaasbeek A, Dekker FW, Maan AC, Swenne CA, et al. Incremental prognostic value of an abnormal baseline spatial QRS-T angle in chronic dialysis patients. Europace. 2013;15:290-6.
27. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic predictors of incident congestive heart failure and all-cause mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006;113:481-9.
28. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006;113:473-80.
29. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J. 2003;24:1357-64.
30. Triola B, Olson MB, Reis SE, Rautaharju P, Merz CN, Kelsey SF, et al. Electrocardiographic predictors of cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. J Am Coll Cardiol. 2005;46:51-6.
31. Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM, Group AR. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). Am J Cardiol. 2007;100:844-9.
32. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.

33. Cuspidi C, Facchetti R, Bombelli M, Sala C, Tadic M, Grassi G, et al. Does QRS Voltage Correction by Body Mass Index Improve the Accuracy of Electrocardiography in Detecting Left Ventricular Hypertrophy and Predicting Cardiovascular Events in a General Population? J Clin Hypertens. 2016;18:415-21.
34. Angeli F, Verdecchia P, Iacobellis G, Reboldi G. Usefulness of QRS voltage correction by body mass index to improve electrocardiographic detection of left ventricular hypertrophy in patients with systemic hypertension. Am J Cardiol. 2014;114:427-32.
35. Robinson C, Woodiwiss AJ, Libhaber CD, Norton GR. Novel Approach to the Detection of Left Ventricular Hypertrophy Using Body Mass Index-Corrected Electrocardiographic Voltage Criteria in a Group of African Ancestry. Clin Cardiol. 2016;39:524-30.
36. Norman JE Jr., Levy D. Adjustment of ECG left ventricular hypertrophy criteria for body mass index and age improves classification accuracy. The effects of hypertension and obesity. J Electrocardiol. 1996;29 Suppl:241-7.
37. Man S, Rahmattulla C, Maan AC, Holman E, Bax JJ, van der Wall EE, et al. Role of the vectorcardiogram-derived spatial QRS-T angle in diagnosing left ventricular hypertrophy. J Electrocardiol. 2012;45:154-60.

APPENDICES

NEDERLANDSE SAMENVATTING

Introductie

Obesitas is momenteel een groot gezondheidsprobleem in ontwikkelde landen. Wereldwijd, en ook in Nederland, is de afgelopen jaren de prevalentie van obesitas toegenomen[1]. Er wordt geschat dat in 2016 bijna de helft (49.2%) van de volwassen Nederlandse populatie overgewicht had (body mass index ≥25 kg/m^2) en dat 14.2% van de volwassenen een BMI had van ≥30 kg/m^2 [2]. Deze percentages zijn veel hoger dan in 1990, toen 33% van de Nederlandse populatie overgewicht en 5.5% obesitas had [2]. Obesitas is geassocieerd met verschillende negatieve gevolgen, zoals cardiovasculaire ziekten, type 2 diabetes mellitus en chronisch nierfalen [3-5]. Er is veel onderzoek gedaan naar de onderliggende pathosfysiologie van aan obesitas gerelateerde ziekten, maar volledig begrepen wordt deze nog niet. De Nederlandse Epidemiologie van Obesitas (NEO) studie is opgezet met het doel om meer inzicht te krijgen in de verschillende paden die leiden naar aan obesitas gerelateerde ziekten. Bij het onderzoek dat in dit proefschrift beschreven wordt, is gebruikt gemaakt van baseline-data van de NEO studie, en er wordt gefocust op de relatie tussen obesitas en cardiometabole en cardiovasculaire afwijkingen.

In de NEO studie zijn er bij de deelnemers verschillende maten van lichaamsvet bepaald. Naast de wat gemakkelijker te bepalen maten zoals body mass index en middelomtrek, werd middels MRI in ongeveer 35% van de studie populatie abdominaal subcutaan en visceraal vet gemeten. Daardoor was het mogelijk om verschillende maten van lichaamsvet en de verdeling hiervan te onderzoeken. Dit is relevant gezien de functie van vet en de cardiometabole gevolgen van accumulatie hiervan kunnen verschillen afhankelijk van de locatie in het menselijk lichaam waar het vet zich bevindt [6-9]. Ook werd er bij alle NEO deelnemers een electrocardiogram gemaakt.

Hieronder wordt een samenvatting gegeven van het beschreven onderzoek in dit proefschrift.

Overzicht van het beschreven onderzoek

In hoofdstuk 2 worden associaties beschreven tussen maten van lichaamsvet en de verdeling hiervan en cardiometabole risicofactoren. De verbanden tussen adipositas en andere cardiometabole risicofactoren worden weerspiegeld in het ‘metabool syndroom’. Het metabool syndroom kan worden gedefinieerd als de clustering van ten minste 3 van 5 cardiometabole risicofactoren in een individu (toegenomen middelomtrek, hoge triglyceriden waarden, lage HDL-cholesterol waarden, hoge bloeddruk of hoge glucose waarden) [10], en is geassocieerd met cardiovasculaire ziekten [11]. Voor de ontwikkeling van het metabool syndroom is obesitas een belangrijke onderliggende risicofactor. In het bijzonder vet dat accumuleert in het intra-abdominale gebied, visceraal vet, is beschreven als een sleutelfactor in de link tussen obesitas en verschillende cardiometabole afwijkingen, zoals insulineresistentie en hypertriglyceridemie [8]. De accumulatie van visceraal vet is geassocieerd met een verhoogde afgifte van vrije vetzuren in de portale circulatie, leidend tot een verhoogd risico op hepatische insulineresistentie [12]. Ook worden er verschillende cytokines uitgescheiden door visceraal vet die de ontwikkeling van metabole verstoringen bevorderen [12]. In hoofdstuk 2 vinden we in mannen en vrouwen met obesitas dat de

verhouding tussen middelomtrek en heupomtrek, de middelomtrek en het viscerale vet geassocieerd zijn met een verhoogd cardiometabool risico, terwijl subcutaan vet daarmee niet geassocieerd is. Visceraal vet, dat abdominale obesitas weerspiegelt, was het sterkst geassocieerd.

Electrocardiografie is goedkoop en wordt veel gebruikt in de klinische praktijk, zowel voor prognostische als diagnostische doeleinden. In hoofdstuk 3 onderzochten we of individuen met het metabool syndroom, maar zonder bekende cardiovasculaire ziekten, van wie we verwachten dat ze een verhoogd cardiovasculair risico hebben, al subtiele verschillen vertonen in electrocardiografische parameters, vergeleken met individuen zonder het metabool syndroom. De electrocardiografische parameters die we hebben onderzocht zijn eerder in verband gebracht met een verhoogd risico op verschillende cardiovasculaire afwijkingen [13-20]. We vonden meer subklinische cardiovasculaire ziekte, bepaald aan de hand van deze electrocardiografische parameters, in individuen met het metabool syndroom dan in individuen zonder het metabool syndroom. We observeerden meer subklinische cardiovasculaire ziekte met elke extra component van het metabool syndroom. We vonden vergelijkbare resultaten in individuen met body mass index ≥30 kg/m^2 en in individuen met body mass index <30 kg/m^2. Middelomtrek was het sterkst geassocieerd met de electrocardiografische parameters.

Om de relatie tussen lichaamsvet en electrocardiografische parameters verder te onderzoeken, onderzochten we in hoofdstuk 4 de associaties van zowel maten van algemene adipositas als abdominale adipositas met electrocardiografische parameters die wijzen op subklinische cardiovasculaire ziekten (in individuen zonder bekende cardiovasculaire ziekten). In de NEO studie zijn er in een grote groep mensen verschillende maten van lichaamsvet en de verdeling daarvan gemeten. Daarom konden we body mass index, totaal lichaamsvet en subcutaan vet onderzoeken als maten van algemene obesitas en middelomtrek en visceraal vet als maten van abdominale obesitas. We vonden dat zowel maten van algemene als van abdominale adipositas geassocieerd zijn met electrocardiografische parameters, wijzend op meer subklinische cardiovasculaire ziekte. Dit is beschreven in hoofdstuk 4. Maten van abdominale adipositas waren niet sterker geassocieerd met subklinische ziekte dan dat maten van algemene obesitas waren.

De associaties tussen maten van lichaamsvet en electrocardiografische parameters wijzen op mogelijke toegevoegde warde van het meenemen van maten van lichaamsvet in diagnostiek die gebaseerd is op electrocardiografie of in huidige cardiovasculaire risico predictie tools. In hoofdstuk 7 verkenden we de bruikbaarheid van het meenemen van maten van lichaamsvet in de electrocardiografische detectie van linker ventrikel hypertrofie. Zoals eerder gezegd, wordt electrocardiografie veel gebruikt in de klinische praktijk. In hoofdstuk 5 en 6 onderzochten we specifieke electrocardiografische variabelen in meer detail.

Hoofdstuk 5 focust zich op de borderline Q-golf, die gezien kan worden op een electrocardiogram. Van een grote abnormale Q-golf wordt gedacht dat deze het resultaat kan zijn van ischemie en dus aanwezig kan zijn na een myocardinfarct, maar ook in schijnbaar gezonde individuen (bij stille ischemie) [21]. In de klinische praktijk wordt een minder abnormale Q-golf, of borderline Q-golf, vaak beschouwd als niet-afwijkend, zeker wanneer

er geen andere electrocardiografische afwijkingen zijn (dan genoemd een geïsoleerde borderline Q-golf). We vonden een slechter cardiovasculair risicoprofiel (hogere leeftijd, alcohol inname, bloeddruk en nuchtere glucose waarden) in individuen met geïsoleerde borderline Q-golven, dan in individuen zonder abnormale Q-golven. Het cardiovasculaire risicoprofiel was het slechts wanneer de borderline Q-golf samenging met andere electrocardiografische afwijkingen (niet-geïsoleerde borderline Q-golven). Verschillende maten van lichaamsvet, en in het bijzonder maten van abdominale adipositas, waren hoger in individuen met geïsoleerde borderline Q-golven en nog hoger in individuen met niet-geïsoleerde borderline Q-golven. Ook waren polsgolfsnelheid en intima-media dikte van de arteria carotis communis hoger in individuen met niet-geïsoleerde Q-golven dan in individuen zonder Q-golven.

In hoofdstuk 6 beschrijven we van verschillende cardiovasculaire risicofactoren dat deze geassocieerd zijn met een wijdere ruimtelijke QRS-T hoek, welke ventriculaire electrofysiologische heterogeniteit reflecteert. Deze bevindingen zijn in lijn met wat eerder in de literatuur is beschreven [22-28]. Ook vonden we een wijdere ruimtelijke QRS-T hoek in individuen met type 2 diabetes mellitus, maar ook in individuen met verhoogde en licht verhoogde nuchtere plasma glucose waarden, vergeleken met individuen met een normaal glucose metabolisme. We lieten ook zien dat zowel intima-media dikte in de arteria carotis communis, een maat van subklinische atherosclerose, en polsgolfsnelheid, een maat van vaatstijfheid, geassocieerd zijn met een wijdere ruimtelijke QRS-T hoek. Zoals verwacht werden deze associaties zwakker na het adjusteren voor cardiovasculaire risicofactoren, waarvan het aannemelijk is dat deze gemeenschappelijke oorzaken zijn van zowel verhoogde intima-media dikte, als polsgolfsnelheid, als een wijdere ruimtelijke QRS-T hoek.

In hoofdstuk 7 lieten we zien dat het electrocardiografisch vaststellen van linker ventrikel hypertrofie door middel van conventionele electrocardiografische criteria verbeterd kan worden door body mass index en de extra electrocardiografische parameter ruimtelijke QRS-T hoek mee te nemen. Linker ventrikel hypertrofie geeft een verhoogd risico op slechtere cardiovasculaire uitkomsten en gezien electrocardiografie goedkoop is en veel gebruikt wordt in de klinische praktijk, is de verbetering van de electrocardiografische vaststelling van linker ventrikel hypertrofie gewenst. In de NEO studie populatie is van alle deelnemers een electrocardiogram beschikbaar en is bij een subgroep van de deelnemers (ongeveer 15%) het hart in beeld gebracht door middel van MRI. Dit heeft het mogelijk gemaakt dat we MRI als referentiestandaard konden gebruiken voor de bepaling van linker ventrikel hypertrofie.

REFERENTIES

1. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. New Engl J Med. 2017;377:13-27.
2. https://www.volksgezondheidenzorg.info/onderwerp/overgewicht/cijfers-context/huidige-situatie#node-overgewicht-volwassenen.
3. Wormser D, Kaptoge S, Di Angelantonio E, Wood AM, Pennells L, Thompson A, et al. Separate and combined associations of body-mass index and abdominal adiposity with cardiovascular disease: collaborative analysis of 58 prospective studies. Lancet. 2011;377:1085-95.
4. Kovesdy CP, Furth S, Zoccali C. Obesity and kidney disease: hidden consequences of the epidemic. Rev Med Chil. 2017;145:281-91.
5. Singh GM, Danaei G, Farzadfar F, Stevens GA, Woodward M, Wormser D, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PloS one. 2013;8:e65174.
6. Bjorntorp P. Adipose tissue distribution and function. Int J Obes. 1991;15 Suppl 2:67-81.
7. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev. 2010;11:11-8.
8. Despres JP. Is visceral obesity the cause of the metabolic syndrome? Ann Med. 2006;38:52-63.
9. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007;116:39-48.
10. Grundy SM. Metabolic syndrome scientific statement by the American Heart Association and the National Heart, Lung, and Blood Institute. Arterioscler Thromb Vasc Biol. 2005;25:2243-4.
11. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. Am J Med. 2006;119:812-9.
12. Bergman RN, Kim SP, Catalano KJ, Hsu IR, Chiu JD, Kabir M, et al. Why visceral fat is bad: mechanisms of the metabolic syndrome. Obesity. 2006;14 Suppl 1:16S-9S.
13. Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, et al. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. Am J Epidemiol. 1999;149:853-62.
14. Dhingra R, Pencina MJ, Wang TJ, Nam BH, Benjamin EJ, Levy D, et al. Electrocardiographic QRS duration and the risk of congestive heart failure: the Framingham Heart Study. Hypertension. 2006;47:861-7.
15. Rabkin SW, Mathewson FA, Tate RB. The relationship of marked left axis deviation to the risk of ischemic heart disease. Int J Cardiol. 1981;1:169-78.
16. Moss AJ. Measurement of the QT interval and the risk associated with QTc interval prolongation: a review. Am J Cardiol. 1993;72:23B-5B.
17. Magnani JW, Johnson VM, Sullivan LM, Gorodeski EZ, Schnabel RB, Lubitz SA, et al. P wave duration and risk of longitudinal atrial fibrillation in persons >/= 60 years old (from the Framingham Heart Study). Am J Cardiol. 2011;107:917-21 e1.
18. Rautaharju PM, Nelson JC, Kronmal RA, Zhang ZM, Robbins J, Gottdiener JS, et al. Usefulness of T-axis deviation as an independent risk indicator for incident cardiac events in older men and women free from coronary heart disease (the Cardiovascular Health Study). Am J Cardiol. 2001;88:118-23.
19. Li Y, Shah AJ, Soliman EZ. Effect of electrocardiographic P-wave axis on mortality. Am J Cardiol. 2014;113:372-6.

20. Higashiyama A, Hozawa A, Murakami Y, Okamura T, Watanabe M, Nakamura Y, et al. Prognostic value of q wave for cardiovascular death in a 19-year prospective study of the Japanese general population. J Atheroscler Thromb. 2009;16:40-50.
21. Kwong RY, Sattar H, Wu H, Vorobiof G, Gandla V, Steel K, et al. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. Circulation. 2008;118:1011-20.
22. de Torbal A, Kors JA, van Herpen G, Meij S, Nelwan S, Simoons ML, et al. The electrical T-axis and the spatial QRS-T angle are independent predictors of long-term mortality in patients admitted with acute ischemic chest pain. Cardiology. 2004;101:199-207.
23. Voulgari C, Tentolouris N, Papadogiannis D, Moyssakis I, Perrea D, Kyriaki D, et al. Increased left ventricular arrhythmogenicity in metabolic syndrome and relationship with myocardial performance, risk factors for atherosclerosis, and low-grade inflammation. Metabolism. 2010;59:159-65.
24. Whang W, Shimbo D, Levitan EB, Newman JD, Rautaharju PM, Davidson KW, et al. Relations between QRS|T angle, cardiac risk factors, and mortality in the third National Health and Nutrition Examination Survey (NHANES III). Am J Cardiol. 2012;109:981-7.
25. Voulgari C, Moyssakis I, Perrea D, Kyriaki D, Katsilambros N, Tentolouris N. The association between the spatial QRS-T angle with cardiac autonomic neuropathy in subjects with Type 2 diabetes mellitus. Diabet Med. 2010;27:1420-9.
26. Atsma F, Bartelink ML, van der Schouw YT, Kors JA, Grobbee DE. Elevated blood pressure and electrocardiographic frontal T axis and spatial QRS-T angle changes in postmenopausal women. J Electrocardiol. 2008;41:360-4.
27. Yamazaki T, Froelicher VF, Myers J, Chun S, Wang P. Spatial QRS-T angle predicts cardiac death in a clinical population. Heart rhythm. 2005;2:73-8.
28. Voulgari C, Tentolouris N, Moyssakis I, Dilaveris P, Gialafos E, Papadogiannis D, et al. Spatial QRS-T angle: association with diabetes and left ventricular performance. Eur J Clin Invest. 2006;36:608-13.

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Curriculum Vitae

Theodora (Dorine) Willemine Elffers werd op 13 augustus 1995 geboren te Haarlem. In 2012 behaalde zij cum laude haar gymnasiumdiploma aan het Driestar College in Gouda, waarna zij aan de studie Geneeskunde begon aan de Universiteit van Leiden. In 2015 behaalde zij haar bachelor geneeskunde en het Honours College-certificaat. Tijdens haar bachelor volgde zij het MD/PhD-traject en in 2016 kreeg zij van de Raad van Bestuur van het Leids Universitair Medisch Centrum een beurs voor 2 jaar promotieonderzoek. In 2016 begon zij als promovenda op de afdelingen Cardiologie en Klinische Epidemiologie, onder begeleiding van Dr. S. Trompet, Prof. dr J.W. Jukema en Prof. dr F.R. Rosendaal. In dit proefschrift zijn de resultaten van het promotieonderzoek beschreven. Tijdens het promotietraject presenteerde zij de resultaten van dit onderzoek op verschillende nationale en internationale congressen. Voor de registratie als epidemioloog B volgde zij tijdens het promotietraject verschillende epidemiologische cursussen. In 2018 begon zij met de coschappen, als onderdeel van de master geneeskunde.

List of Publications

Burggraaf JL, **Elffers TW**, Segeth FM, Austie FM, Plug MB, Gademan MG, Maan AC, Man S, de Muynck M, Soekkha T, Simonsz A, van der Wall EE, Schalij MJ, Swenne CA. Neurocardiologic differences between musicians and control subjects. *Netherlands Heart Journal* 2013; 21:183-8

Elffers TW, de Mutsert R, Lamb HJ, Maan AC, Macfarlane PW, Willems van Dijk K, Rosendaal FR, Jukema JW, Trompet S. Association of metabolic syndrome and electrocardiographic markers of subclinical cardiovascular disease. *Diabetology and Metabolic Syndrome* 2017; 9:40

Elffers TW, de Mutsert R, Lamb HJ, de Roos A, Willems van Dijk K, Rosendaal FR, Jukema JW, Trompet S. Body fat distribution, in particular visceral fat, is associated with cardiometabolic risk factors in obese women. *PLoS One* 2017; 12:e0185403

Elffers TW, de Mutsert R, Lamb HJ, Maan AC, Macfarlane PW, Willems van Dijk K, Rosendaal FR, Jukema JW, Trompet S. Relation of Overall and Abdominal Adiposity With Electrocardiogram Parameters of Subclinical Cardiovascular Disease in Individuals Aged 45 to 65 Years (from the Netherlands Epidemiology of Obesity Study). *The American Journal of Cardiology* 2018; 121:570-578

Elffers TW, Trompet S, Maan AC, Lamb HJ, Macfarlane PW, Rosendaal FR, Jukema JW. Borderline Q-waves in individuals without overt cardiovascular disease: Relations with adiposity, subclinical atherosclerosis and vascular stiffness. *International Journal of Cardiology* 2019;274:331-336

Elffers TW, Jukema JW. De onvoorspelbaarheid van coronaire atherosclerose. *Nederlands Tijdschrift voor Geneeskunde* 2018; 162:D2109