

Obesity and Cardiovascular disease. Results from the Netherlands Epidemiology of Obesity Study Elffers, T.W.

Citation Elffers, T. W. (2019, January 9). *Obesity and Cardiovascular disease. Results from the Netherlands Epidemiology of Obesity Study*. Retrieved from https://hdl.handle.net/1887/67913

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Author: Elffers, T.W.Title: Obesity and Cardiovascular disease. Results from the Netherlands Epidemiology of Obesity StudyIssue Date: 2019-01-09

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 \geq 25 kg/m²) and that 14.2 % of adults had a body mass index of \geq 30 kg/m², 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/m²) 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/m²)	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. Measure- ment 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}.





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 threedimensionally 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⁻ 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 \geq 27 kg/m² 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/huidigesituatie#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.
- 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 metaanalysis. 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- Frank E. An accurate, clinically practical system for spatial vectorcardiography. Circulation. 1956;13:737-49.
- 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.
- 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.

- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.