

Evaluation of Published Clinical Scores for the Prediction of Cardiometabolic Risk in the SEMEOTICONS Project

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Abstract: Cardiovascular and metabolic diseases are the major causes of morbidity and mortality in the Western Countries. Metabolic syndrome (defined as 3 out of 5 factors among increased waist circumference, hypertension, high blood glucose, high triglyceride and low high density lipoprotein (HDL) cholesterol concentrations) is associated with increased cardiometabolic risk. Other indexes have been proposed and validated, based on the measurement of plasma concentration of lipids, glucose and liver enzymes. In the SEMEOTICONS project we plan to measure parameters related to increased cardiometabolic risk, e.g. skin accumulation of cholesterol and advanced glycated end products, liver enzyme alteration by changing in skin and eye color and obesity. The results will allow to evaluate cardiometabolic risk using non invasive clinical parameters. The new score obtained will be compared with previously validated indexes. In this paper we have evaluated the most common cardiometabolic risk scores i.e., VAI (Visceral Adiposity Index), HTG- Waist (Hypertriglyceridemic Waist), FLI (Fatty Liver Index) and LAP (Lipid Accumulation Product), that we will use during the project.

1 INTRODUCTION

Obesity prevalence is rapidly increasing and together with it there is a global increase in the risk of developing related diseases, e.g., type 2 diabetes mellitus (T2DM), atherosclerosis, hypertension, hyperlipidemia, coronary artery disease and in general cardiovascular diseases (CVD). The assessment of risk of disease is becoming important not only to prevent the development of co-related diseases and complications through an early intervention but also to maintain a good quality of life. Moreover, risk reduction is important for controlling the national health expenditure, through prevention of people not at risk, intervention to prevent complications, reduction of cases of hospitalization of patients at risk.

It is important to become self-conscious of potential risk factors. Technology can help in evaluating individual risk and in promoting changes in lifestyle that can reduce risk of disease.

Signs derivable from face observation are a potential source of health information, e.g. for fat

accumulation, liver dysfunction, hypercholesterolemia, hyperlipidemia, cardiovascular homeostasis and general psychophysical status. Once properly mapped to computational descriptors, systematic exploitation of face signs and their change over time will allow to build an effective self-monitoring system. In this perspective, in the frame of the FP7 ICT project SEMEOTICONS (SEMEiotic Oriented Technology for Individual's Cardiometabolic risk self-assessment and Self-monitoring), the most relevant face signs of cardiometabolic risk are reviewed and analyzed so as to drive their detection, quantification and integration into a virtual individual model useful for cardiometabolic risk prevention. In particular here we are reviewing the most common used indexes that will be also evaluated in the project and tested against the data on face signs of cardiometabolic risk obtained in the SEMEOTICONS project.

2 CARDIOVASCULAR RISK

Atherosclerotic cardiovascular diseases (CVDs), including heart disease and stroke, are the leading causes of mortality worldwide (World Health Organization, 2008). Clinical manifestations of atherosclerotic disease are detected only when they are advanced stages. One of the major risk factor for atherosclerosis is related to impaired in glucose metabolism, especially high postprandial glucose even in non diabetic subjects (Andreozzi et al., 2013). Moreover alterations in glucose and lipid metabolism are also associated with an increased risk of endothelial dysfunction, decreased diastolic function, but also increased risk of myocardial infarction and stroke. Altogether, frequently, the major events, such as serious health complications, disability and death can occur between 40 and 60 years of age. CVDs represent one of the major challenges to the health systems since the majority of patients who survive a myocardial infarction do not fully recover the ventricular function, and many stroke survivors have physical limitation in the daily activities. This explains the importance to prevent and treat even early clinical manifestations of CVDs.

Among the most common risk scores for coronary heart disease (CHD) and CVD there are the Framingham score (Grundy et al., 1998) derived in the general population in the USA that estimates the 10 year CHD risk and the SCORE (Systematic COronary Risk Evaluation for High & Low cardiovascular Risk) proposed by the European Society of Cariology (Perk et al., 2012) tha evaluates the 10 year fatal CVD event. The SCORE uses age, smoking, total cholesterol and systolic blood pressure. The Framingham score uses the same parameters of the SCORE plus diastolic blood pressure, high density lipoprotein (HDL) cholesterol and presence of diabetes. Both scores use different cut off for males and females. The SCORE has the advantage of having different charts for different countries to better estimate the risk. These scores need the use of charts to build up the score or the use of online calculators. However, neither the Framingham nor the SCORE can be used to predict the metabolic risk but only the CVD risk.

3 CARDIOMETABOLIC RISK

Main cardiometabolic risk factors are listed in Table 1 and divided among modifiable and non-modifiable. Among the strongest modifiable risk factors for cardiometabolic diseases there are obesity

(defined as a BMI>30 kg/m²), hypertension (increased systolic and/or diastolic blood pressure), hyperlipidemia (ie, increased concentrations of triglyceride and/or total cholesterol and/or decreased concentrations of HDL cholesterol). (Kissebah et al., 1989); (Despres et al., 1990); (Pouliot et al., 1992); (Carey et al., 1997); (Turkoglu et al., 2003). The risk is even higher in subjects with abdominal obesity (i.e., with increased waist circumference), and it is independently associated with increased age-adjusted risk of CVD, even after adjusting for BMI and other cardiovascular risk factors (Carey et al., 1997); (Rexrode et al., 1998); (Rexrode et al., 2001).

Table 1: Main cardiometabolic risk factors.

Modifiable factors		Non-modifiable factors
Overweight/Obesity	Smoking	Age Race/Ethnicity Gender Family History
High LDL cholesterol	Unhealthy eating	
Low HDL cholesterol	Health disparities	
High triglycerides	Physical inactivity	
hyper-coagulation	Psychosocial issues	
High blood glucose		
Hypertension		
Inflammation		

3.1 Metabolic Syndrome (MS)

It has been recognized that subjects at risk to develop type 2 diabetes and CVD tended to have not only high blood pressure, fasting glucose and low HDL, as recognized by the Framingham study, but also increased waist circumference and triglyceride concentration. Since these parameters cluster together it has been proposed to define this clinical condition as metabolic syndrome (MS) when at least 3 out of 5 factors are above the normal range (NCEP-ATPIII, 2001); (Alberti et al., 2006); (Alberti et al., 2009) (Table 2) and identify the subjects at risk of developing type 2 diabetes and/or CVD. After the initial general ranges proposed in 2001 (NCEP-ATPIII, 2001) different cut offs for the parameters described have been proposed (see Table 2). More importantly the IDF has recognized that different cut offs for waist circumference identify the risk in the European compared to the American or Asian subjects. Although widely criticized these definitions are widely used (Ferrannini, 2007).

3.2 Ectopic Fat and Cardio-metabolic Risk

Cardiometabolic risk is associated not only to

Table 2: Criteria for diagnosis of Metabolic Syndrome.

	NCEP ATP III CRITERIA (2001)		IDF CRITERIA (2005)	
	Men	Women	Men	Women
Waist (cm)	>102	>88	>94 (EU) >102 (USA)	>80 (EU) >88 (USA)
HDL (mg/dl)	<40	<50	<40	<50
Triglycerides (mg/dl)	≥150		≥150	
BP (mm Hg)	≥130/≥85		≥130/≥85	
FPG (mg/dl)	≥110		≥100*	

•ATPIII criteria 2001: 3 or more risk factors
 •IDF criteria 2005: Central obesity (ethnic specification) plus any two of the other 4 factors
 •AHA/IDF/IAS/IASO 2009: 3 abnormal findings out of 5 IDF2005 criteria would qualify a person for the metabolic syndrome. Different cut points for waist depending on regions

general obesity but also to abdominal obesity, i.e., the preferential fat accumulation as visceral fat ectopic fat in liver, heart, pancreas and muscle. Both visceral and ectopic fat accumulations are associated to the presence of insulin resistance, increased lipolysis, release of free fatty acid, very low density lipoprotein (VLDL), proinflammatory factors as cytokines, C reactive protein and fibrinogen, decreased cardiac function, atherosclerosis, endothelial dysfunction and decreased carotid elasticity (Figure 1).

Visceral, cardiac and ectopic fat accumulation can be evaluated using imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) but this is feasible only in a research setting. Surrogate measures for abdominal fat is waist circumference that is linearly related to the amount of visceral fat. Ectopic fat is associated with lipotoxicity and organ dysfunction, so for example alteration in liver enzymes are often associated with triglyceride accumulation in the liver, high cholesterol is a major risk factor for atherosclerosis, increased triglyceride is associated with both alteration in liver and cardiac metabolism. (Morelli et al., 2013)

Although the MS recognizes the importance of abdominal obesity in the stratification of cardiometabolic risk it does not include any parameter related to liver function, i.e., alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT). Several studies have shown that not only abdominal obesity but also hepatic steatosis clusters with the parameters of CVD and is a recognized risk factor for the development of cardiometabolic diseases (Anstee et al., 2013); (Morelli et al., 2013).

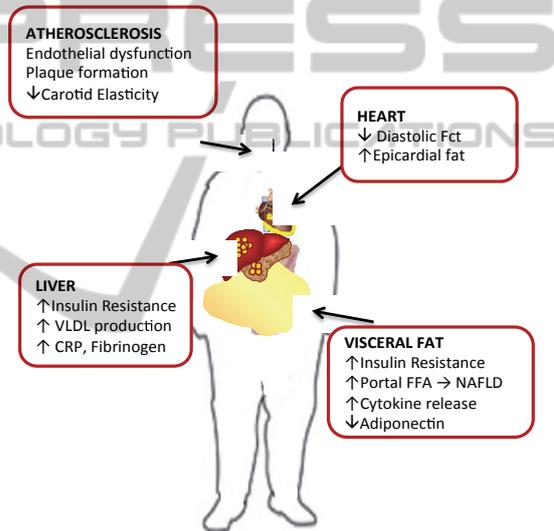


Figure 1: Accumulation of visceral fat, hepatic and cardiac fat as well as atherosclerosis and plaque formation are major risk factors for cardiovascular and metabolic diseases.

Assessment of hepatic steatosis and of cardiometabolic risk associated could be done using scores recently developed, i.e., Fatty liver index (FLI), visceral adiposity index (VAI), hypertriglyceridemic waist (HTG-Waist) or lipid accumulation product (LAP).

Impaired glucose metabolism is associated with the formation of advanced glycated end-products, known also as AGEs, that are believed to play a causative role in the blood-vessel complications of diabetes mellitus by speeding up oxidative damage to cells and in altering their normal behaviour. These harmful compounds can affect nearly every type of cell and molecule in the body and are thought to be

one factor in aging and in some age-related chronic diseases.

3.3 Indexes of Cardiometabolic Risk

There are several indexes that have been validated as score for risk of cardiometabolic disease. VAI (visceral adiposity index) (Amato et al., 2010); (Petta et al., 2010); (Petta et al., 2012), HTG-Waist (Hypertriglyceridemic Waist Phenotype) (Lemieux et al., 2007); (Blackburn et al., 2009); (de Graaf et al., 2010), LAP (Lipid Accumulation Product) (Kahn, 2005); (Bedogni et al., 2010); (Ioachimescu et al., 2010), FLI (Fatty Liver Index) (Bedogni et al., 2006); (Gastaldelli et al., 2009); (Balkau et al., 2010); (Kozakova et al., 2012).

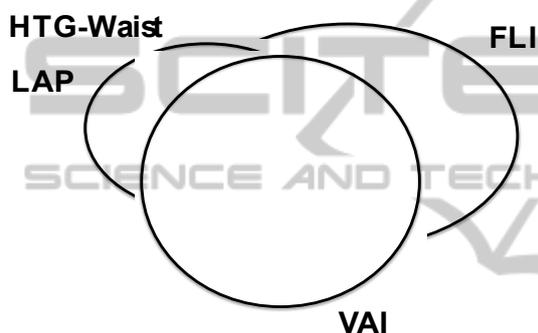


Figure 2: Variables used in the most reliable cardiometabolic risk scores cluster together and resembled factors of metabolic syndrome.

These scores have the advantage of using continuous values of clinical variables (except the HTG-Waist index) instead of cut offs to assess risk for CVD, T2DM or in general cardiometabolic diseases and they return a continuous value. They are based on clinical parameters generally acquired during medical routine control visits (e.g., weight, height, BMI, waist circumference, blood pressure, plasma concentrations of triglyceride, cholesterol and glucose).

These indexes are widely used in research settings individually but, to the best of our knowledge, there isn't an independent comparison of their ability to predict cardiometabolic risk or incidence of type 2 diabetes or cardiovascular or cerebrovascular events. For this reason we decided to evaluate all of them in the SEMEOTICONS project. It is clear looking at figure 2 that there is quite an overlap in the calculation of the indexes and that they all use TG and waist circumference. If the addition of BMI and/or GGT and/or HDL is adding power to the ability of prediction of risk it is not known.

In the following paragraphs we report the way to calculate the indexes and their ability in determining cardiometabolic risk. It is important to remark that all indexes have been developed in the general or healthy population and their use in patients with type 2 diabetes or other diseases has to be confirmed. In the SEMEOTICONS project we will also evaluate subjects without known disease either cardiovascular or metabolic.

3.3.1 VAI (Visceral Adiposity Index)

The VAI (visceral adiposity index) was developed in a population of over 300 healthy non obese subjects and then validated in a risk population (Amato et al., 2010). It is calculated using different formulas for men and women and is based on waist circumference (WC in cm), body mass index (BMI), triglyceride concentration (TG in mg/dl) and HDL cholesterol concentration (in mg/dl).

$$\text{male: } (WC/39.68 + (1.88 \times BMI)) \times TG/1.03 \times 1.31/HDL \quad (1)$$

$$\text{female: } (WC/36.58 + (1.89 \times BMI)) \times TG/0.81 \times 1.52/HDL \quad (2)$$

Normal values are $VAI < 1$ in healthy nonobese subjects with normal adipose distribution and normal TG and HDL cholesterol levels.

The VAI has been shown to be related to increased insulin resistance, cardiovascular and cerebrovascular events, liver fibrosis and steatosis in patients with NAFLD and hepatitis C (Amato et al., 2010); (Petta et al., 2010); (Petta et al., 2012).

3.3.2 HTG-Waist (Hypertriglyceridemic Waist Phenotype)

It is calculated using different values for men and women with a cut off for waist circumference (WC in cm), and triglyceride concentration (TG in mg/dl) (i.e., it is not a continuous score).

3 groups with different risk have been identified:

Group 1 (low waist circumference and low triglycerides): waist ≤ 90 cm in men or ≤ 85 cm in women and triglyceride < 177 mg/dl

Group 2 (high waist circumference and low triglycerides): waist circumference > 90 cm in men or > 85 cm in women and triglycerides < 177 mg/dl

Group 3 (high waist circumference and high triglycerides): waist circumference > 90 cm in men or > 85 cm in women and triglycerides ≥ 177 mg/dl

This index has been found associated not only with a deteriorated cardiometabolic risk profile but also with an increased risk for coronary artery disease

(Arsenault, Lemieux et al. 2010).

3.3.3 LAP (Lipid Accumulation Product)

This index has been developed in the general population (i.e., the third National Health and Nutrition Examination Survey) (Kahn, 2005) and identifies cardiometabolic disorders and depends on the measurement of WC and fasting triglycerides (expressed in mmol/l). The formulas are different for men and women:

$$\text{men} = (\text{WC [cm]} - 65) \times (\text{triglycerides [mmol/L]}) \quad (4)$$

$$\text{women} = (\text{WC [cm]} - 58) \times (\text{triglycerides [mmol/L]}) \quad (5)$$

The diagnosis of enlarged waist elevated TG syndrome can be evaluated by considering the cut off utilized for the definition of MS (see table 2) that for Europe will become

Europeans: Men=LAP>50, Women = LAP>38

Americans: Men=LAP>63, Women = LAP>51

Considering the different cut offs for waist circumference.

The index has been validated in the Dionysos population (the same used to develop the Fatty liver index FLI) as a marker of steatosis (Bedogni et al., 2010) and has been shown to be associated with increased cardiometabolic risk and metabolic syndrome (Taverna et al., 2011) and predicted mortality in a population of nondiabetic patients at high risk for cardiovascular diseases (Ioachimescu et al., 2010).

3.3.4 FLI (Fatty Liver Index)

This index has been developed in the general population (Bedogni et al., 2006). Compared to the previous indexes here reviewed the FLI does not discriminate by gender and it is calculated using waist circumference (WC in cm), body mass index (BMI), triglyceride concentration (TG in mg/dl) and GGT concentration (in mg/dl) using the formula:

$$\frac{e^{(0.953 \times \ln \text{TG} + 0.139 \times \text{BMI} + 0.718 \times \ln \text{GGT} + 0.053 \times \text{WC} - 15.745)}}{(1 + e^{(0.953 \times \ln \text{TG} + 0.139 \times \text{BMI} + 0.718 \times \ln \text{GGT} + 0.053 \times \text{WC} - 15.745)})} \times 100 \quad (3)$$

The score is varying between 0 and 100. Three groups with different risk have been identified:

Group 1 = FLI ≤20 probability not to have FL >90%

Group 2 = FLI: 21-59, intermediate group

Group 3 = FLI ≥60 probability to have FL > 78%.

Although GGT is used in the calculation of FLI, the

index was not dependent on alcohol intake (Gastaldelli et al., 2009). High FLI values have been associated also to early carotid plaques (Kozakova et al., 2012) and increased mortality (Calori et al., 2011).

4 SEMEOTICONS PROJECT

The central idea SEMEOTICONS project is to exploit the face as a major indicator of individual's wellbeing for the prevention of cardio-metabolic risk and cardiovascular diseases. In accordance to a semeiotics viewpoint, face signs will be mapped to measures and computational descriptors, automatically assessed. Detection and integration of signs derived from the semeiotics of the face can be used to build sensitive equipment to self-monitor the physical state, evaluate the risk of disease and elaborate suggestions useful for optimizing life style through personalized changes. SEMEOTICONS's main technological objective is to develop a multisensory system hosted into a hardware platform having the exterior aspect of a conventional mirror (*Wize Mirror*). The latter will be equipped with cameras and depth sensors to analyse face morphology. That will provide, among other things, descriptors of facial physiognomy with respect to obesity traits. In addition, the *Wize Mirror* will include multispectral cameras working with a dedicated lighting system for image acquisition, UV light to stimulate fluorescence mechanisms, and thermal lamps for heat testing of endothelial function. Beside morphological description of the face, the implemented system will allow obtaining data on the cardio-respiratory system (heart rate, blood-oxygen saturation, endothelial function, respiratory rate), on the presence of products of glucose and lipid metabolism in the skin, and the evaluation of colour of face and eyes that could be related to alteration in liver enzymes (Hentges and Huerter, 2001); (Pejic and Lee, 2006).

In the *Wize Mirror*, integration of multisensory data will exploit an innovative Virtual Individual Model (VIM) whose development is a main methodological objective in SEMEOTICONS. A set of objective signs, closely related to cardiometabolic risk profile assessed from unobtrusive examination of the face will drive the temporal evolution of VIM defining a subject's well-being status. To track the evolution VIM status, we will implement a so-called Well Being Index (WBI), which is conceived as a multidimensional score mapping the VIM status to different risk's components (i.e. cardiovascular risk,

metabolic risk, lifestyle-habits risks).

To reach methodological and technological objectives, clinical scores of cardiometabolic risk have a twofold role: they provide a path to develop the new indices for cardiometabolic risk and offer a well-established basis to validate the system.

It is worth noting that several signs observed by the Wize Mirror are related to the parameters used in the risk scores shown in Figure 2.

During the validation part of the project we plan to evaluate the association of metabolic parameters with the measured clinical parameters in order to evaluate the new cardiometabolic risk scores (i.e. WBI components) made available by the *Wize Mirror* platform.

5 CONCLUSIONS

In recent years, self-monitoring and self-training approaches to personalized strategies for the cardiometabolic risk prevention have experienced growing interest from both the scientific community and health care systems.

In this context, medical semeiotics offers a sound methodological frame to build new computational tools also exploiting innovative multi-sensing devices. The rich variety of signs detectable in an individual's face is particularly attractive to implement effective methods for self-assessment of individuals' health status. The integration of computational descriptors of well-established face signs (e.g. expressive traits, morphometric and colorimetric features) with new measurements of physiological quantities (e.g. skin cholesterol, AGE concentration, heart and respiratory rates, analysis of exhaled gases) is an important step towards *digital semeiotics*. In view of that, the existing charts of cardio metabolic risk offer significant clues and provide meaningful indications to researchers and system developers. At the same time, they remain essential tools to validate self-monitoring activity.

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