

PREGLED LITERATURE – REVIEW ARTICLE

**Cardiovascular risk prediction in children - with focus on obesity**

Rizik od kardiovaskularnih bolesti kod gojazne dece

**Bojko Bjelakovic<sup>1,2</sup>**

<sup>1</sup>Clinic of Paediatrics, Clinical Center, Nis, Serbia

<sup>2</sup>Medical Faculty, University of Nis

**Summary** The majority of children at risk for future cardiovascular disease who need specific and systematic cardiovascular risk assessments are obese children. However, there are still many unresolved questions related to pathophysiology, recognition and management of obese children. Currently, the most prevalent paradigm for identifying children at risk for cardiovascular events is based on the population approach and identification of the level and/or number of traditional risk factors. However risk assessment methods based on, traditional risk factors solely have proven to be suboptimal and unreliable. Since early atherosclerosis commonly occurs in the absence of abnormal threshold levels of risk factors, the traditional risk factors based approach has recently shifted to "individual-based approach". Such a new concept is focused on the identification of asymptomatic structural target organ changes or more recently subclinical functional cardiac or vascular target organ changes to identify children at risk.

**Keywords:** cardiovascular risk, children, obesity

**Sažetak** Većina dece sa rizikom za prevremeni nastanak kardiovaskularnih bolesti (KVS) jesu gojazna deca. Danas postoji još uvek puno kontradikcija vezano za patofiziologiju KVS bolesti u gojazne dece, njihovu pravovremenu dijagnostiku i način terapije. Trenutna doktrina u kliničkom pristupu gojaznoj deci se sastoji u identifikaciji broja i nivoa tradicionalnih faktora rizika. Ovakav pristup može biti prilično nepouzdan i zbog toga se sve više teži ranom prepoznavanju i kvantifikaciji subkliničkih organskih promena koje prethode KVS morbidnim događanjima. U radu će biti prikazane aktuelne dileme vezane za rizik stratifikaciju gojazne dece sa osvrtom na rizik predikciju KVS bolesti u odraslih.

**Cljučne reči:** kardiovaskularni rizik, deca, gojaznost

**Introduction**

It is a general truth that correct prediction in everyday life appears to be more of the exception rather than the rule. This is especially obvious for future individual health prediction, particularly future cardiovascular risk (CV) prediction in obese individuals which often turns out to be wrong or widely inaccurate.

The majority of children at risk for future cardiovascular disease who need specific and systematic cardiovascular risk assessments are obese children with metabolic syndrome (MetS) (1,2,3). However, there are still many unresolved questions related to pathophysiology, recognition and management of obese children. The remoteness of incident CVS morbid events from general cardiovascular health in childhood many years beforehand, makes the relationship of cardiovascular health status in childhood with cardiovascular events later in life hardly feasible (4).

Currently, the most prevalent paradigm for identifying children at risk for cardiovascular events is based on the population approach and identification of the level and/or number of traditional risk factors(1,5). However risk assessment methods based on, traditional risk factors solely have proven to be suboptimal and unreliable. It was clearly shown that statistical approaches to determine the influence of traditional risk factors (markers) on the occurrence of CVS diseases are over-simplified and inadequate for that purpose. By relying on such markers many high risk children are overlooked and left untreated, and many low risk children are inappropriately targeted for treatment(6). Since early atherosclerosis commonly occurs in the absence of abnormal threshold levels of risk factors, the traditional risk factors based approach has recently shifted to "individual-based approach".

Such a new concept is focused on the identification of asymptomatic structural target organ changes or more recently subclinical functional cardiac or vascular target

organ changes to identify children at risk. Of note, this approach is not only clinically proven but also biologically justified (7).

Surprisingly we routinely still don't take into account structural or functional target organ (TO) changes which are a necessary precondition and intermediate end points for developing CV morbid events regardless of the level of target risk factor.

Assessment of arterial structure and function as well as endothelial function together with assessment of left ventricle geometry and function are some of the potentially useful clinical approaches for early identification of children at increased cardiovascular risk (8, 9, 10).

To summarize, although much of currently recommended medical practice and essentially all evidence-based practice assume the application of population mean effects to individuals, we should try to change our view on this topic from statistical to more biologically approach.

### **Population based cardiovascular risk assessment model in adults. How does it work?**

Almost all current CV risk prediction models (both for children and adults) are based on multivariable regression equations derived from different cohorts in which the levels of traditional or non-traditional risk factors are assigned points to predict CVS outcome (11, 12, 13). In fact we are usually measuring a number of different parameters (metabolic or genetic biomarkers, anthropometric parameters, environmental factors) without having knowledge of their biological meaning in real sense. Although we are cognizant that there is a statistical relation between risk factor and CVS events, it is still not quite clear are they just in casually or casual association with future CVS outcome. Furthermore, the most of the currently used cardiovascular risk prediction models in adults are devised for older individuals (>40 year) having perhaps well-established cardiovascular disease or high life time risk, but low 10-years risk (12).

If we look at the most relevant CVS risk scoring models in adults: Framingham heart study, European Systematic Coronary Risk Evaluation (SCORE), Prospective Cardiovascular Munster (PROCAM) model Reynolds Risk Score, it is not so hard to conclude that strategies based on risk factors measurements are not the best way to select individuals at increased CV risk.

In prospective Atherosclerosis Risk in Communities Study (ARIC) study in adult patients who develop coronary heart disease less than one forth were classified in high risk category, with Framingham risk scores greater than 20 %. Moreover, overall 70 % or more of individuals who developed coronary heart disease have low or medium Framingham risk scores (14, 15). Another, highly cited study by Sachdeva et al, focused on singular traditional risk factors assessment in adults hospitalized with acute coronary artery disease, showed that almost 77 % of patients had normal values of LDL, (below 130 mg/dl), 61,8 % had normal values of triglyceride (below 150 mg/dl) and 45,4 % had normal values of HDL (>40 mg/dl)(16). Study by Futterman et al. also reported the similar percentage

of patients (near 50%) without any of the conventional risk factors, developing coronary artery disease (17).

Recently, many authors have tried to improve risk prediction by adding novel recently characterized putative risk factors such as inflammatory and thrombogenic biomarkers. Most notably, lipoprotein(a), C-reactive protein, uric acid, interleukin-6, fibrinogen, plasminogen-activator-inhibitor 1 (PAI-1) levels, serum amyloid A and P, fibrinogen, BM: I-CAM1, V-CAM1, selectin E, von Willebrand factor (18).

All of them are closely related with body fat mass and are markedly elevated in most patients with obesity but don't add much to improve CVS risk prediction over the currently established predictive models.

This is also the case with genetic biomarkers added to conventional risk factor algorithms, such as 9p21 risk alleles which additive benefit was small. Although initially looked very promising, after considering the strength of the available evidence any screening for genetic CAD risk variants or any clinical use of algorithms based on genetic scores are not recommend to calculate future CV risk (19).

The most relevant criticism of any given doctrine based on the traditional cardiovascular factor assessment is that risk prediction models provide risk estimates for populations but not individuals.

Recently Joshi and Nasir found considerable heterogeneity between risk factors and atherosclerotic burden as measured by coronary calcium score. They have reported that in high-traditional risk groups with 0 CAC, the event rates are consistently low and in traditional low-risk groups with elevated CAC (CAC>100), the event rates are consistently high.(20) Of note, to data there are no randomized clinical trials showing that all currently used risk assessment guidelines might improve CVS outcome (21).

### **Cardiovascular risk assessment in obese children**

Although the relationship between adult obesity and cardiovascular disease (CVD) has been shown in adults, the relationship of childhood obesity and cardiovascular disease in adulthood remains unclear. On the other hand the relationship between singular or multiple traditional risk factors in childhood with CVS outcome is well established.

It is demonstrated that about one third of obese children have metabolic syndrome (MetS) which is the name for a group of risk factors dyslipidemia, hypertension, insulin resistance, that raises risk for CVD and other health problems both in children and adults (3). Several different MetS scores and algorithms which predict adult cardiometabolic risk in children have been developed, but diagnostic test results against a clinical outcome, such as CVD, have not been published for most of them, and they have not been validated in other populations. Although we presume that the critical duration of exposure to these risk factors may accumulate at an earlier time point, resulting in premature signs of cardiovascular disease there are no studies to date have directly assessed the impact of MetS on cardiovascular disease outcome. Only Magnussen et al. found that youth with MetS had 2 to 3 times the risk of having high cIMT and T2DM as adults compared with those

free of MetS at youth (22). Of note, obesity alone was shown to have similar predictive value as presence of metabolic syndrome MetS itself (22).

The most comprehensive study investigating the long term influence of obesity on CVS outcome in adulthood involved 276,835 Danish school children for whom measurements of height and weight were available. The risk of any coronary heart disease event, a nonfatal event, and a fatal event among adults was positively associated with BMI at 7 to 13 years of age for boys and 10 to 13 years of age for girls. The associations were linear for each age, and the risk increased across the entire BMI distribution. Furthermore, the risk increased as the age of the child increased (23).

On the other hand, systematic review done by Lloyd et al. have challenged the previously accepted view that the presence of childhood obesity is an independent risk factor for CVD and that this period should be a priority for public health intervention (24). They have found little evidence to suggest that childhood obesity is an independent risk factor for CVD risk. Correspondingly the next systematic review on this issue also provides little evidence to suggest that childhood overweight and obesity are independent risk factors for metabolic and cardiovascular risk during adulthood. Instead, the data demonstrate that the relationships observed are dependent on tracking of BMI between childhood and adulthood, alongside persistence of dietary patterns and physical activity. Unexpectedly, adjustment for adult BMI uncovered unexpected negative associations between childhood BMI and adult disease, suggesting a protective effect of childhood obesity at any given level of adult BMI (25).

Nevertheless, autopsy studies and few observational studies have shown that CVS risk factors typical for MetS are related to the development of atherosclerosis. One of the most striking of the findings in the Bogalusa study has clearly established the significant risk factors in youth, well described in about 1000 publications and four books (26).

Magnussen et al. studied changes in adiposity (BMI, waist circumference, skinfold thickness), fitness (bicycle testing), plasma lipids (TC, LDL-C, HDL-C, TG), smoking and socioeconomic status (parental education level) in 539 young Australians in the Childhood Determinants of Adult Health Study (1).

Baseline measurements were made in 1985 when participants were 9, 12, and 15 years old, and again between 2004 and 2006. Among those with hypertriglyceridemia in youth, 79% of males and 97% of females had normal values 20 years later. The majority of those with elevated levels of HDL-C at follow-up had normal levels at baseline. Both TC and LDL-C tended to be more constant, and most youngsters with elevations at baseline had them at follow-up, later in life (27).

When participants had adverse lipid profiles at baseline, gained weight, or continued to smoke at follow-up, they were more likely to have dyslipidemia as well. Similarly, those without adverse lipid profiles at baseline were significantly more likely to have dyslipidemia later if they gained weight or continued to smoke in the interim. Last, those who had normal lipid profiles at baseline, but who developed higher risk at follow-up had greater gains in weight, reduced fitness, and failed to rise socioeconomically.

Also, of note was the association of long-term aerobic exercise training and upward social mobility from youth to adulthood, with higher HDL-C levels. The data suggested that, whether dyslipidemia was present or not in youth, risk factor modification significantly impacted risk when those individuals became adults some 20 years later. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) studied 2,876 persons 15–34 years of age who died of external causes, and found a strong concordance between coronary and aortic atherosclerosis and risk factors. The early PDAY score of modifiable risk factors and its variation predict risk in youth and may be useful in identifying high risk individuals. Recent imaging studies reflect the same pathophysiology.

The Cardiovascular Risk in Young Finns study sought to determine whether childhood risk factors were associated with a 6-year change in carotid intima media thickness (CIMT) in young adulthood independent of the current risk factors. In 1,809 subjects who were followed for 27 years from baseline (in 1980, age 3–18 years), CIMT was measured both in 2001 and 2007. Childhood risk factors assessed included LDL-C, HDL-C, BP, obesity, diabetes, smoking, physical activity, and frequency of fruit consumption. In participants with zero, one, two, and  $\geq$ three risk factors, CIMT increased during 6 years by 35, 46, 49, and 61  $\mu\text{m}$  ( $P = 0.0001$ ) (28). This relationship remained significant after adjustment for adulthood risk. Of the individual childhood variables, physical inactivity and infrequent fruit consumption were associated with accelerated CIMT progression after adjusting for the adult risk factors. The associations of childhood lipid values and BMI with CIMT progression became non significant when adjusted for current (adulthood) risk factor levels. In those risk factors with greater relative importance of adult values—HDL/LDL ratio and obesity—correction of adverse childhood factors in adulthood appeared to attenuate the ill effects of childhood burdens suggesting that interventions to improve lipid and weight abnormalities between youth and adulthood would be productive. International Childhood Cardiovascular Cohort (I3C) consortium investigated the age at which risk factors influenced CIMT later in adulthood. The analyzed parameters of 4380 participants included total cholesterol, blood pressure, BMI, triglycerides measured from age 3–18 years, and CIMT measured in adulthood ages 20–45 years, mean follow-up 22.4 years. The number of childhood risk factors was predictive of higher CIMT when measured at ages 9, 12, 15, and 18 years with higher probability of a raised CIMT as number of risk factors increased.

## **Conclusion**

Similar to CVS risk prediction in adults, currently, the most prevalent paradigm for identifying obese children at high risk for cardiovascular events is based on the identification of the same conventional (traditional) population risk factors and estimation of number and level of these factors. However the association between risk factors and CVS event rates is continuous at all levels of the risk factors and the slope of risk is modest. So the current recommendation to treat risk factors when levels exceed a

certain threshold is neither statistically nor medically justified. Furthermore, the relationship between risk factors and early disease is dependent in large part on intrinsic individual differences in response to risk factors which is inherited and might some day be detectable in genomic analyses. On the other hand, it is rational to conclude that so called risk factors for morbid CVS events are actually risk factors for functional and structural abnormalities of arteries and heart likely to precede occurrence of CVS morbid events. The question is, do we need to follow previous doctrine and try to find another promising marker more specific and sensitive for future CVD and wait another 40 or 50 years for hard CVS outcome to occur, or we should try to change our concept and look at the presence of other pathology substrate likely to progress to CV morbid events.

Left ventricular mass and carotid intima media thickness are nowadays widely chosen as the physiological parameters of interest because their structural alterations precede the development of atherosclerosis and have been correlated with other risk factors for coronary heart disease regardless of risk factors. The only handicap is that information on structural cardiovascular alterations (are suggestive of more established disease) than the incipient mainly functional changes.

We are also now enlightened with proofs that endothelial function represents an integrative index of both "overall CV risk burden factors burden and the sum of all vasculoprotective factors in an individual. Considering that endothelial dysfunction is a well-established response to cardiovascular risk factors and precedes the development of atherosclerosis it is likely that the status of an individual endothelial function may be a missing link between cardiovascular risk factor burden and the propensity to develop atherosclerotic disease.

Over the past decades many methodological approaches have been developed to measure the pathophysiological function of the endothelium in humans and it seems that endothelial function measurement which is now possible may lead to much better estimation of CVS risk and identification of high risk patients. A few of these methods are easily applied in adults and children and have a fair reproducibility.

However no standard recommendation exist, and different method used in research limited ability to make comparison and generalization of reported finding so additional data are needed before these methods can be adopted in clinical evaluation (29–31).

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**Correspondance to:**

Bojko Bjelakovic M.D., Ph.D. Assoc. Prof.,  
Clinic of Paediatrics, Clinical Center, Nis  
Zorana Đindica 48 Boulevard, 18000 Nis, Serbia  
bojko968@gmail.com