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# Novel and Traditional Cardiovascular Risk Factors in Adolescents

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## 1. Introduction

Cardiovascular diseases are prevalent conditions which impose significant negative impacts on the healthcare system. According to World Health Organization (WHO), non-communicable diseases (NCD) including cardiovascular diseases account for more than 60% of all deaths globally. Overweight/obesity, diabetes, hypertension and dyslipidemia are all traditional cardiovascular risk factors in adults. Of particular concern, adolescence obesity and its associated cardiovascular risk and co-morbidities have substantial tracking into adulthood (1-4).

Advances in technology of agriculture have helped to increase food production resulting in easily available, excessive provision of food in many developed countries. Urbanization also leads to changes in leisure activities from doing sports to television viewing and computer games. As a consequence to increasing demand from school and leisure activities, sleep deprivation is another novel risk factor contributing to the escalation of cardiovascular risk in the youth populations. In addition, exposure to heavy metals is increasingly recognized as a consequence of urbanization and may contribute to premature atherosclerosis.

## 2. Traditional cardiovascular risk factors in adolescents

### 2.1 Overweight and obesity

Overweight/obesity is an important and well-known cardiovascular risk factor in children, adolescents and adults. Obesity is closely associated with clustering of cardiovascular risk factors with insulin resistance being the possible link(5). Obesity is also associated with increased risk of a number of co-morbidities and premature mortality in both adult and the youth populations (2, 6-11). In a British cohort followed up for 57 years, overweight in childhood was associated with 1.5 times increased risk of all-cause mortality and two-fold increased risk of ischemic heart disease (6). Co-morbidities of adolescence obesity include type 2 diabetes mellitus, micro-inflammation, atherogenic dyslipidemia, hypertension, left ventricular hypertrophy, premature atherosclerosis leading to cardiovascular diseases,

obstructive sleep apnoea, gastroesophageal reflux disease, depression and other psychosocial abnormalities (2, 12-16). Clustering of traditional cardiovascular risk factors, namely metabolic syndrome, is noted to have ethnic disparities (17) and the prevalence also varies according to the different definitions of metabolic syndrome adopted (11, 18). Despite the controversies regarding the exact definitions of metabolic syndrome in both adults and children (19, 20), International Diabetes Federation (IDF) recently suggests abdominal obesity as the core criteria in making a diagnosis of metabolic syndrome (21), highlighting the pivotal role of obesity in linking these cardiometabolic abnormalities and cardiovascular diseases.

Childhood obesity can predict the cardiovascular risk in adulthood (22). With increasing childhood obesity, there is increasingly early onset of atherosclerosis (23). In a study involving Hong Kong Chinese overweight children aged 9-12 years (mean BMI  $25 \pm 3$  kg/m<sup>2</sup>), BMI was independently associated with impaired arterial endothelial function and increased carotid intimal medial thickness, which are early markers of atherosclerosis (24). An important message from this study is that these obesity-related early vascular dysfunctions are partially reversible by lifestyle modifications (25).

Prevalence of childhood and adolescence overweight/obesity has marked variation among developed and developing countries. The prevalence of childhood and adolescence obesity has tripled between 1980 and 2000 in United States (US) and doubled between 1985 and 1995 in Australia (26). In a systemic review of published literatures examining data of prevalence of overweight/obesity among children living in developing countries, lowest prevalence was found in India and Sri Lanka whereas highest prevalence was found in Eastern Europe and the Middle East (27). When comparing epidemiological and clinical studies examining childhood and adolescence overweight/obesity, the diagnostic criterion used to define overweight/obesity should be interpreted with cautions. Despite the importance to identify overweight/obese individuals and screen for associated cardiovascular risk factors early, there is no consensus regarding the diagnostic criteria of childhood and adolescence obesity (28). Compared to adults, assessment of overweight and obesity in children and adolescents are different and not that straightforward. We need to take growth and puberty into consideration because BMI is anticipated to change with age and depends on gender. Gender difference is particularly important in the assessment of childhood and adolescence obesity as girls and boys enter puberty at different pace. In children and adolescents, there are ongoing debates regarding the optimal cutoff values of BMI and waist circumference (WC) to define childhood and adolescence overweight and obesity with various diagnostic criteria adopted by different countries and authorities (28-32).

From published pediatric literatures, at least four diagnostic criteria have been used for the definition of overweight and obesity in children and adolescents (11, 28):

1. An international BMI-for-age reference curve for defining overweight and obesity in children 2 to 18 years of age by the US National Center for Health Statistics, Centers for Disease Control and Prevention (CDC) and the International Obesity Task Force (IOTF) in 2000 (IOTF criteria) (31).

These criteria were based on median BMI by age and gender in six nationally representative datasets from Brazil, Hong Kong, Netherlands, Singapore, United Kingdom (UK) and the US from an international growth survey in 2000. These surveys had over 10,000 subjects

each and altogether covered 97,876 boys and 94,841 girls. Overweight and obesity were defined as BMI-for-age  $\geq 25$  and  $\geq 30$  kg/m<sup>2</sup> respectively.

2. A national BMI reference curve for Chinese children and adolescents reported by the Group of China Obesity Task Force (COTF) in 2004 (COTF criteria) (33).

These criteria were based on the Chinese National Survey on Students Constitution and Health in 2000 involving 244,200 primary and secondary Chinese students aged 7–18 years. Overweight and obesity were defined as BMI-for-age  $\geq 24$  and  $\geq 28$  kg/m<sup>2</sup> respectively.

3. CDC 2000 Growth Charts for the US (CDC criteria) (34).

These criteria were based on the US National data collected in a series of 5 surveys between 1963 and 1994 for children and adolescents aged 2–20 years. Overweight and obesity were defined as BMI-for-age  $\geq 85^{\text{th}}$  and  $\geq 95^{\text{th}}$  percentiles respectively.

4. The Hong Kong Growth Survey (HKGS) conducted in 1993 with sex-specific reference charts of weight-for-height (HKGS criteria) (35).

This was a territory-wide cross-sectional growth survey which covered around 25,000 Hong Kong Chinese children from birth to 18 years of age. Childhood obesity in this survey was defined as weight > median weight for height  $\times 120\%$ . No definition for childhood overweight was set in this survey.

In recent years, increasing clinical attention has been drawn to central obesity because central body fat is a better predictor than overall body fat for cardiovascular risk factors in both adults (36, 37) and children (7, 38, 39). Central obesity reflects excess visceral adiposity which is a major culprit for insulin resistance and associated cardiovascular disease in both adults and children (7, 38, 40–43). WC and WC-derived indexes such as waist-to-hip ratio (WHR) and waist-to-height ratio (WHTR) are commonly employed anthropometric measurements as proxy measures of central obesity. In Caucasian adults, WC  $\geq 102$ cm in men and  $\geq 88$ cm in women are used to define central obesity (1,3). The corresponding cutoff values in Chinese and South Asian men and women are  $\geq 90$ cm and  $\geq 80$ cm respectively (5, 44). In adults, there are at least 14 different methods to quantify WC (19). In pediatric literatures, measurements of WC have been described at 5 different sites: 1) midway between the lowest rib and superior iliac crest (45–49); 2) at the umbilical level (50, 51); 3) at the narrowest point of the torso (52); 4) at the level of the right upper iliac crest (53); and 5) at the level of 2 cm above the umbilicus (54). Based on the 2005/2006 Hong Kong Growth Survey including 14,842 Hong Kong Chinese school children aged 6 to 18 years, reference values and percentile curves for WC and WHTR are established (49). These charts are based on WC measured midway between the lowest rib and superior iliac crest and provide reference values for estimation of central obesity in local Hong Kong Chinese youth populations.

In summary, adolescence obesity is a global concern because obesity associated cardiovascular risk factors and abnormalities are potentially reversible in early disease stage. Despite the epidemic of childhood and adolescence obesity worldwide, the most appropriate criterion to ascertain the diagnosis is still inconclusive. Given the high rates of adolescence obesity, adolescents are important population for monitoring and intervention.

## 2.2 Diabetes

Diabetes is a disorder of glucose metabolism with complex interplays between genetic, lifestyle and environmental factors. Historically, type 2 diabetes is much less common in children and adolescents compared to autoimmune type 1 diabetes and type 2 diabetes has once been thought to be non-existent in children (55). However, with increasing prevalence of obesity worldwide, type 2 diabetes in children and adolescents is increasing at an alarming pace (55). Atherosclerosis starts in young people with type 2 diabetes (56). The general awareness of type 2 diabetes in adolescents should be escalated, particularly in those with obesity and family history of type 2 diabetes. American Diabetes Association (ADA) (57) has recommended the testing for type 2 diabetes in asymptomatic children and adolescents who are: aged 10 years or at onset of puberty, overweight (BMI >85<sup>th</sup> percentile for age and sex, weight for height >85<sup>th</sup> percentile, or weight >120% of ideal for height), plus any two of the following risk factors:

1. family history of type 2 diabetes in first- or second-degree relative;
2. race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander);
3. clinical evidence and/or association of insulin resistance, e.g. polycystic ovarian syndrome, metabolic syndrome, acanthosis nigricans, etc;
4. maternal history of gestational diabetes during the child's gestation.

ADA recommends a three yearly screening in these at-risk young individuals (57). In making the diagnosis of diabetes in adolescents, the possibility of "hybrid" disease with obesity and concomitant diseases with compromised insulin secretion such as maturity-onset diabetes of the young (MODY) or latent autoimmune diabetes in adult (LADA) should always be considered (58).

For adolescents with type 1 diabetes who present with acute decompensation and diabetic ketoacidosis (DKA), insulin therapy is the standard therapy. Insulin use is also advised in youth with type 2 diabetes who present with severe hyperglycemia ( $\geq 11.1$  mmol/L),  $HbA_{1c} > 8.5\%$  or severe manifestation of insulin deficiency such as DKA (59). Although oral antidiabetic agents are not recommended in treatment of type 1 diabetes traditionally, metformin use in conjunction with insulin in adolescents with poorly controlled diabetes has been reported to improve their glycemic control (60). Despite the escalating rate of type 2 diabetes in the youth, therapeutic modalities remain limited with metformin being the only U.S. Food and Drug Administration (FDA)-approved oral treatment for youth with type 2 diabetes (61). Similar recommendation has been adopted in other countries (62).

## 2.3 Hypertension

The global epidemic of obesity is leading to a shift in the diabetes, as well as hypertension distribution towards increasing levels in children and adolescent (63, 64). In addition, physical inactivity and high salt/sodium intake contribute to the rise in the prevalence of hypertension in the youth. Similar to childhood and adolescence obesity, there is also tracking of high blood pressure from childhood into adulthood (65, 66). Autopsy findings from Bogalusa Heart Study and the Pathobiologic Determinates of Atherosclerosis in Youth (PDAY) have shown that higher blood pressure in the youth populations is associated with increased atherosclerosis (67, 68).



Accurate measurement of blood pressure and correct diagnosis of hypertension or pre-hypertension in the youth populations are important to prevent end-organ damage in adults. The fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents has suggested a diagnosis of hypertension as >95<sup>th</sup> percentile for gender, age and height on  $\geq 3$  occasions. Stage 1 hypertension is diagnosed if systolic or diastolic blood pressure reaches 95<sup>th</sup> to 99<sup>th</sup> percentile plus 5 mmHg on at least 3 separate occasions(69) whereas stage 2 hypertension is defined as >99<sup>th</sup> percentile plus 5mmHg. Various diagnostic cutoff values have been suggested for defining hypertension and pre-hypertension in the youth population (Table 1). Pre-hypertension is defined as >120/80 mmHg or  $\geq 90^{\text{th}}$  to <95<sup>th</sup> percentile (69). Blood pressure increases with age, yet there is limited information regarding the time course for children and adolescents with pre-hypertension to progress to hypertension. For early diagnosis of pre-hypertension and hypertension, reference blood pressure standards by sex-, age-, weight- and height are clinically important (70, 71).

The 4 <sup>th</sup> report on the diagnosis, evaluation, and treatment of high BP in children and adolescents(69)	Cool et al (76) , (77) and Kong et al (39, 78)	Cruz et al (79) and de Ferranti et al (75)	Weiss et al (80)	Zimmet et al (21)
BP > 95 <sup>th</sup> percentile for gender, age and height on $\geq 3$ occasions	BP $\geq 90^{\text{th}}$ percentile for gender, age and height	BP > 90 <sup>th</sup> percentile for gender, age and height	BP > 95 <sup>th</sup> percentile for gender, age and height	BP $\geq$ 130/85 mmHg

Table 1. Diagnostic criteria used in pediatric literatures for definition of hypertension. Blood pressure: BP.

White coat hypertension is a well recognized phenomenon of transiently high blood pressure related to stress. Home-clinic blood pressure difference can vary substantially by age in children with the difference reduced with advancing age and substantially diminished after 12 year-old(72). Therefore, ambulatory blood pressure (AMBP) is gaining popularity in both children and adults due to the stronger correlation between high AMBP with target organs damage observed in an emerging number of studies in both adults and paediatric populations (73).

For youth with pre-hypertension and hypertension, a search and thorough evaluation for secondary causes is recommended as secondary hypertension is more common in children than adults(69). If secondary hypertension is ruled out, children and adolescents with pre-hypertension should start lifestyle modifications(69). For stage 2 hypertension, drug therapy should be initiated but for those with stage 1 hypertension, pharmacological treatment is recommended if symptomatic, evidence of end-organ damage, concomitant diabetes or persistent high blood pressure despite non-pharmacological measures(69). A detailed elaboration of the dosage, dosing interval and precautions of different types of antihypertensive drugs for children with hypertension has been described in the fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents(69).

## 2.4 Dyslipidemia

Dyslipidemia continue to track from childhood into adulthood(74). Similar to the controversies in diagnosis of obesity and hypertension, there is no consensus regarding the definition of dyslipidemia in children and adolescents. Typical dyslipidemia in children and adults with obesity and insulin resistance include increased triglyceride and decreased high-density lipoprotein (HDL) cholesterol levels. The definitions of high triglyceride level in the youth range from  $\geq 1.1$  mmol/l (ie  $\geq 100$  mg/dL) (75),  $\geq 1.2$  mmol/l (39, 76, 77) to  $\geq 1.7$  mmol/l (21, 39, 78). Some researchers adopt age-, sex- and/or race-specific percentile cutoff to diagnose hypertriglyceridemia with triglyceride  $\geq 90^{\text{th}}$  percentile (79) and  $>95^{\text{th}}$  percentile (80) used. For defining low HDL cholesterol levels in the pediatric literatures, a cutoff value of  $\leq 1.03$  mmol/l (ie  $< 40$ mg/dL) for all ages/sexes (39, 76-78),  $< 1.03$  mmol/l (21),  $< 1.3$  mmol/l (ie  $< 50$ mg/dL)(75), or gender-specific cutoff  $\leq 1.03$  mmol/l for boys and  $\leq 1.3$  mmol/l for girls (81), or percentile specific cutoff  $< 5^{\text{th}}$  percentile (age-, sex- and race-specific)(80) and  $\leq 10^{\text{th}}$  percentile (age-, sex- and height-specific) (79, 82) have been reported.

Low density lipoprotein (LDL) cholesterol remains to be the primary target of lipid control to prevent cardiovascular events in adults (83). Hence, majority of randomized controlled trials carried out in pediatric populations have also focused on the use of statins in youth with elevated LDL cholesterol levels. There is general consensus that statin should be initiated, in combination with diet and lifestyle modification if LDL cholesterol level  $> 4.1$  mmol/l (ie 160mg/dl) in at-risk youth (84, 85). Fibrates and niacin are lipid lowering drugs targeted to treat high triglyceride and low HDL cholesterol in adults, but neither drugs is approved for use by US FDA in the pediatric population.

## 3. Novel cardiovascular risk factors in adolescents

### 3.1 Sleep

Physiologically, average sleep duration decreases with progression from infancy, childhood to adolescence (86). With increasing demand from school and work, as well as changes in leisure activities such as television watching and computer games, the average sleep duration in the US adults has decreased from 9 hours per night a century ago to 6.9 hours per night in 2005 (87). In Sweden, the average sleep time has decreased from 9 hours per night in 1910 to 7.5 hours in 1990's in adults aged 20-64 years (88).

Sleep deprivation is now increasingly recognized as a lifestyle factor contributing to the global epidemic of childhood obesity and a novel, potentially reversible cardiovascular risk factor. Both laboratory and epidemiological studies suggested associations of obesity, insulin resistance, diabetes and cardiovascular disease with sleep debt in children, adolescents and adults (89-91). Increasing number of epidemiological studies show close association between sleep duration and obesity, which is evident as early as during early childhood (92-96). Short duration of sleep at age of 3 years predict future risk of obesity in childhood (92). In a Japanese study of 8274 children aged 6-7 years, an inverse relationship between hours of sleep and risk of childhood obesity was observed (93). Cross-sectional studies from US, Canada, UK, France, Germany and Japan suggest increased risk for overweight or obesity in Caucasian, Hispanic, African-American and Japanese children who sleep long hours than those with short sleep duration (93, 97-101). Prospective studies also suggest a predictive role of short sleep duration for overweight and obesity in Caucasians

children (92, 102). Similar data from Chinese children and adolescents are comparatively sparse. A recent survey in Taiwan involving 656 boys and girls aged 13-18 years showed that sleep deprivation (defined as sleep <6 hours on schooldays) was associated with poor health status as measured by health-related behaviors in self-reported questionnaires (103).

Although the exact underlying mechanism linking sleep and obesity is not fully understood, preliminary results suggest a possible neurohormonal basis. There is evidence showing that sleep curtailment can activate the hypothalamo-pituitary-adrenal (HPA) axis (104). Van Cauter *et al* have demonstrated a significant rise in plasma cortisol levels in the following evening amongst subjects after partial (0400-0800 hours) and total sleep deprivation (37% and 45% increases,  $p=0.03$  and  $0.003$  respectively) compared to those with normal sleep duration (2300-0700 hours) (104). In another study by Van Cauter *et al*, sleep debt was associated with adverse effects on carbohydrate metabolism and endocrine function (105). Glucose tolerance and thyrotropin concentrations were reduced while evening cortisol concentrations and activity of sympathetic nervous system were increased in the sleep debt group (4 hours per night) (105). Interestingly, these hormonal and metabolic changes are very similar to that accompanying normal ageing. Based on rodent studies, positive relation between sleep curtailment and hyperphagia has been noted. Van Cauter *et al* further demonstrated an inverse relationship between sleep debt and leptin, an important anorexigenic hormone secreted by adipocytes mediating the signals between adipose tissues and the hypothalamic regulatory centers (106, 107). In concert with this phenomenon, elevated ghrelin levels, the orexigenic hormone, were observed with reduced sleep duration accompanied by increased hunger and appetite (106). Similar results have also been reported by other workers showing associations between high BMI, short sleep duration, decreased leptin and elevated ghrelin levels (95). In addition, lipid and energy metabolism are regulated by circadian rhythm (108). Sleep problems may result in dysregulation of lipid metabolism and metabolic syndrome. In a national study in Japan, sleep duration in adults was closely related with serum lipid and lipoprotein levels (109). Recently, an association between atherogenic dyslipidemia and reduced sleep duration is reported in both U.S. and Hong Kong Chinese adolescents (110, 111).

### 3.2 Inflammation

Atherosclerosis can be regarded as a state of chronic, low-grade inflammation of the arterial wall, resulting from the interactions between plasma lipoproteins, peripheral blood mononuclear cells (PBMC) and the endothelium (112). It has been increasingly recognized the clinical utility and prognostic role of serum inflammatory markers levels, in addition to traditional cardiovascular risk factors, in estimating cardiovascular risk in both adults and the youth populations. Both high circulating white cell counts and high serum high sensitivity C-reactive protein (hsCRP) are associated with increased risk of diabetes and associated complications in adults (113, 114). Increasing clinical evidence also suggests a link between inflammation, insulin resistance and cardiovascular risk factors in children and adolescents (13, 115-117). In a school children study including over 2,000 Hong Kong Chinese adolescents (median age: 16 years), overweight/obesity was associated with two to six-fold increased risk of having high hsCRP tertiles (13). In another cross-sectional study including 326 obese children aged 6-12 years (mean age 8.9 years), white blood cell counts were associated with plasma lipid profile (triglyceride, total and LDL cholesterol) and obesity indices (body mass index and WC) (117).



### 3.3 Heavy metals and environmental pollutants

Apart from changes in habits and lifestyle, exposure to heavy metals is increasingly recognized as a consequence of urbanization. Most heavy metals cannot be metabolized by our body, and excessive accumulation in the body will disturb the normal functions of cells. Kidney is the key organ to eliminate heavy metals from the body. Heavy metals might lead to albuminuria through inducing oxidative stress to renal tubular cells(118, 119). Certain heavy metals have additive effect in inducing nephrotoxicity. For example, synergistic effect of arsenic (As) and cadmium (Cd) in causing renal damage has been demonstrated in Chinese general population(120). In addition, chronic exposure to toxic heavy metals may promote atherosclerosis and contribute to the development of chronic kidney disease and cardiovascular diseases (119, 121). Furthermore, air pollutants can provoke systemic pro-inflammatory and pro-thrombotic response and lead to increase in platelet counts and platelet activation(122). The significance of platelet activation and whether anti-platelet therapies can help reducing cardiovascular risk profiles in the youth populations is still a debatable subject(123). Further studies are required to examine the impact of heavy metals and environmental pollutants, as novel cardiovascular risk factors, in accelerating the development of cardiovascular disease in both adults and the youth populations(124).

## 4. Controversies and the unmet needs to be addressed

Lifestyle modification including regular exercise and diet are cornerstones of management of traditional cardiovascular risk factors including obesity, diabetes, dyslipidemia and hypertension. With recent evidence demonstrating the importance of adequate sleep duration in adolescents, education for a healthy sleep habit becomes one of the essential targets of lifestyle modification to prevent cardiovascular risk factors in the youth. Childhood and adolescence are vulnerable periods for habit formation due to substantial tracking of lifestyle habits and cardiovascular risk from this period into adulthood (125, 126). Thus, promoting healthy eating habit, regular exercise and healthy sleep habit in the youth are important strategies to curb the public health problem of obesity.

The optimal dietary approach to combat obesity and reduce cardiovascular risk factors is still a matter of controversies. Indeed, modern food-processing technology produces many food products with high glycemic index (GI). There is now emerging evidence showing that both the quality and quantity of dietary components can impact upon various physiological processes underlying energy metabolism and control of satiety which can provide the basis for dietary intervention in diabetes and obesity (127, 128). Epidemiological studies from US and China indicate that the risks of chronic diseases such as type 2 diabetes and coronary heart disease are strongly related to dietary GI (129, 130). High GI food, especially rice, the main carbohydrate-contributing food in Chinese, may increase risk of diabetes (130). WHO and Food and Agriculture Organization (FAO) recommend low-GI diet to prevent common chronic diseases of affluence, including obesity and type 2 diabetes (131). Recently, it has been suggested that low GI diet may have a role in the management of childhood obesity(132).

Promotion of regular exercise is another important aspect of lifestyle modifications in reducing cardiovascular risk in adolescents. Physical inactivity has been reported to be associated with obesity and other cardiovascular risk factors in adolescents(133). The role of exercise in weight management and control of cardiovascular risk factors is usually

associated with its direct impact on energy expenditure and its potential to alter various components of appetite control and eating behavior. Low physical activity level predicts weight gain in different ethnic groups (134, 135). Regular physical activity maintains good health and prevents myocardial infarction, cardiovascular events and premature mortality (136, 137). Since early 1990s, many studies have demonstrated the beneficial effects of physical activity on promoting weight reduction and fat loss as well as reducing risk of diabetes and hypertension (138-141). Beneficial effects of exercise and diet are possibly beyond weight reduction. In a small scale study of obese Hong Kong Chinese children, combined intervention with diet and exercise reduced adiposity as well as improved lipid profiles and endothelial function compared to diet alone (25). In another study, a 6-week intervention with diet and strength training improved lipid profile in obese Chinese children (142).

WHO recommends regular and accumulated physical activities to prevent premature death and other adverse health outcomes (143). However, there are ongoing debates on the optimal frequency, duration and intensity of physical activity. Most international guidelines recommend moderate activity in adults, especially those who are older and less active (136). In a systematic review of over 850 published literatures, the authors recommended  $\geq 60$  minutes physical activity of moderate to vigorous level in school-age youth (144). In 1988, the American College of Sports Medicine first recommended children and adolescents to have 20-30 minutes of vigorous exercise daily (145). In 2007, the Regional Office for Europe of the WHO made similar recommendations (146). Other guidelines suggested physical activity of moderate intensity at least twice or more weekly to enhance and maintain muscular strength, flexibility and bone health (20) while others suggested high levels and long duration of regular exercise (e.g. daily physical activity lasting at least 90 minutes) in the youth population (147).

As previously discussed, despite the escalating rate of diabetes and dyslipidemia in the youth population, therapeutic modalities remain limited with metformin and statin being the only US FDA approved oral treatment for youth with type 2 diabetes (61, 62) and dyslipidemia respectively (84, 85). More clinical researches are required to demonstrate the efficacy and safety for more therapeutic options in managing adolescents with type 2 diabetes and dyslipidemia.

## 5. Conclusion

In conclusion, cardiovascular disease is an increasing world health problem. In view of the substantial tracking of cardiovascular risk factors from adolescents to adulthood, there is an urgent need to intervene early with efficacious strategies to identify and treat the youth with cardiovascular risk factors. The traditional cardiovascular risk factors, namely overweight/obesity, diabetes, hypertension and dyslipidemia do not account for all cardiovascular deaths and novel factors, including lifestyle (e.g. sleep deprivation) and environmental (e.g. heavy metal poisoning), as well as the consequences and interactions related to these traditional and novel risk factors (e.g. inflammation and platelet activation) appear to be important, accounting for the dramatic recent changes in prevalence and would be of public health concern. Moreover, more intensive program for lifestyle modification and aggressive approach of pharmacological treatment should be considered in the youth at-risk of cardiovascular events.

## Unmet Needs to be addressed in managing CVD risk factors in adolescents

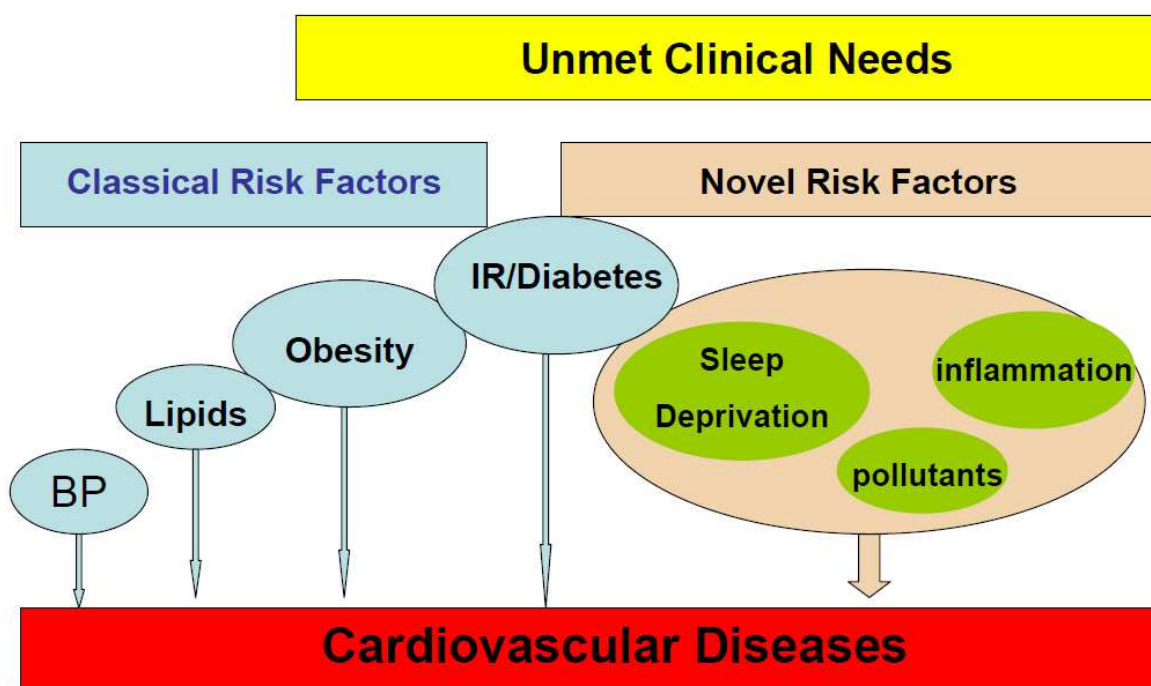


Fig. 1. Traditional and Novel Cardiovascular Risk Factors in Adolescents.

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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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