Page 188 to 198

Volume 1 • Issue 4 • 2017

Review Article

Therapeutic Advances in Cardiology

ISSN: 2575-5161

Metabolic Syndrome and Cardiovascular Implications in Younger People

María Luz Gunturiz Albarracín*

Specialized professional, Public Health Research Division, National Institute of Health, Colombia

***Corresponding Author:** María Luz Gunturiz Albarracín, Specialized professional, Public Health Research Division, National Institute of Health, Colombia.

Received: December 12, 2017; **Published:** December 28, 2017

Abstract

Metabolic syndrome is a multifactorial problem that combines environmental and genetic factors that in young people have a direct impact on the quality of life of the adult. The early identification of risk factors at early ages could first step in the prevention of future complications and to promote adequate lifestyles that reduce the probability and prevalence of chronic diseases such as such as obesity, diabetes mellitus, high blood pressure and accidents cardio cerebrovascular, among others. The purpose of this review is to describe key elements that demonstrate the importance of the detection and control in children and adolescents of metabolic syndrome risk factors from childhood to healthy adulthood.

Keywords: *Metabolic Syndrome; Cardiovascular risk factors; Heart disease; Obesity; Younger people*

Abbreviations

The following abbreviations are used in this manuscript

Met S: Metabolic syndrome; MHO: Metabolically healthy obese; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BMI: Body mass index; CC: Circumference of the abdominal waist; IR: insulin resistance; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; HAE: HDL-apoA-I exchange; DM1: Diabetes mellitus type 1; DM2: Diabetes mellitus type 2; CVD: Cardiovascular disease; IDF: International Diabetes Federation

Volume 1 Issue 4 December 2017

Introduction

Metabolic syndrome (MetS), it is defined as a pool of metabolic disorders including obesity, raised blood pressure, dyslipidemia, and elevated fasting glucose, among others. MetS is one of the most important complications of excess weight, with an increase in the prevalence of obesity and overweight in children and adolescents. The risk factors that characterize it are: obesity of central or abdominal predominance, hypertension, hypertriglyceridemia, hyperglycemia and decrease of the cholesterol bound to high density lipoproteins [1].

This syndrome may be of special interest because of the increased prevalence with age [2-4]. In addition to the predominant criteria to diagnose MS, it is associated with other metabolic abnormalities related to cardiovascular diseases such as, plasma increases in plasminogen activating factor and fibrinogen, hyperuricemia, elevated levels of C-reactive protein, hyperhomocysteinemia, the increase in the expression of tumor necrosis factor alpha in adipose tissue and the decreased concentrations of adiponectin [4-6].

Cardiovascular Risk Factors

For the last decades, much attention has been dedicated to cardiovascular risk factors present in younger people; as a result, the view is increasingly accepted that prevention of the appearance of risk factors and the early manifestations of atherosclerotic and hypertensive cardiovascular diseases requires intervention before adulthood. Despite this knowledge, the risk factor prevalence was found to be high amongst young subjects. Additionally, in several studies have been published response rate, the awareness of high blood pressure, high LDL-C, and TC levels was the lowest in young subjects. Lack of awareness suggests that greater attention to health-related knowledge and behavior, especially among young people, is needed [7].

Studies about longevity population also revealed different types of metabolic disturbances [8-14], being these results variable between countries and ethnics. Instead, centenarians from Poland showed that mildly elevated blood pressure is a marker for better health status [9]. Recent study of familial longevity from China revealed decreased diastolic blood pressure but increased systolic blood pressure in centenarians. Similar discrepancy can also be found among studies of lipid profile and longevity. Biological study for longevity demonstrated that centenarians and their offspring have significantly larger high-density lipoprotein (HDL) levels and particle sizes and low-density lipoprotein (LDL) levels compared with controls (Milman., *et al*. 2014; Barzilai., *et al*. 2003). However, other studies did not find significant association of HDL-C levels with centenarians [12-15].

Several studies including systematic reviews and meta-analyzes have shown that the presence of MetS is associated with an increase in composite cardiovascular disease (CVD), stroke, myocardial infarction, and all-cause mortality. Likewise, the risk of CVD mortality associated with MetS is greater than the risk associated with the individual components of MetS, suggesting that individuals with the large range of metabolic abnormalities associated with MetS should be included in intensive prevention programs primary. Additionally, it has been shown that the development of components of MetS in childhood can be followed in adolescence and adulthood, reinforcing the need for early detection of MetS and of course prevention of cardiovascular diseases [16].

Obesity and Metabolic Syndrome

Obesity, metabolic syndrome and type-2 diabetes mellitus (DM2) are three interrelated conditions that share a number of pathophysiological mechanisms and that are frequently observed to lead, in succession, to cardiovascular complications. The fact that their prevalence is increasing alarmingly should prompt all healthcare professionals urgently to implement measures to prevent these complications. The most effective, though also the least adopted, are those related to lifestyle modification. Drug treatment targeted at controlling risk factors (e.g., hypertension, dyslipidemia, and thrombophilia), metabolic abnormalities, and excess weight is also necessary [17-19].

Obesity represents one of the main health problems in the world. As in most developed countries, the prevalence of obesity in adults is increasing rapidly. For example in Korea [20], a study revealed that 34.9% of men and 30.5% of women were obese. Although it has been widely reported that obesity is closely associated with complications such DM2 and CVD, there is a subset of individuals that appear to be resistant to the development of metabolic abnormalities despite the presence of obesity, which are classified as "metabolically healthy obese (MHO)", and the proportion that varies according to ethnicity, age and level of physical activity. These data could generate confusion about the future risk of developing diabetes, CVD or mortality in subjects with this phenotype. On the other hand, was reported that the elevated risk of all-cause and CVD mortality was only evident in MHO subjects after long-term follow-up (≥ 10 years), suggesting that the duration of follow-up is an essential component to be taken into account when assessing the future risk of developing diabetes and CVD in MHO subjects [1,19,21-22].

Childhood obesity is an independent risk factor for adulthood: an obese child has an 80% chance of remaining so at 35 year old [23]. On the other hand, the adolescent with excess weight, even though it was thin, has a relative risk of 1.8 mortality from any cause and 2.3 mortality from cardiovascular causes in adulthood compared to normal weight adolescents [1,21].

In addition, the prognostic implication of obesity may differ with age. Several epidemiological studies have suggested that the risk of excess mortality associated with obesity is weak or reversed in elderly subjects [20,22]. In spite of this, the impact of the MHO phenotype on the future metabolic risk according to age group has not been previously investigated.

Body size and metabolic phenotype are unstable and the transition to a different metabolic state often occurs over time [24,25]. Therefore, the future metabolic risk relative to the baseline phenotype may be a sum of changes in phenotypes during follow-up. To clearly determine if the MHO phenotype poses a metabolic risk, it is necessary to differentiate the risk of subjects experiencing changes in their phenotype from those who maintain this phenotype during defined study periods, although, in most studies, effects of chronological changes or duration of exposure to phenotypes of metabolic BMI on morbidity or mortality, making difficult the determination and characterization of cardio metabolic risk in MHO individuals [6].

In the literature worldwide, various forms of characterization of MetS have been reported in children and adolescents with a similar meaning to adult MetS. There are several difficulties in defining a MetS definition in the childhood and adolescence accepted and generalized that include, measurements of HDL cholesterol, triglycerides, abdominal waist and blood pressure, ethnic differences, the use of unique normative values for different pediatric ages, the fact that alterations in metabolic indicators in most children are quantitatively moderate, the absence of a range of normality for insulin in infancy and the physiological IR of puberty. Applied studies in obese children and adolescents have shown how the changes introduced in MetS definitions determine the prevalence of the disease, which would vary between 15 and 50% depending on the criteria used. In addition, because MetS is directly related to obesity, the prevalence of MetS increases as that increase the prevalence and severity of obesity [6, 26-28].

There are different definitions of metabolic syndrome; the first was published by the World Health Organization (WHO), later, other associations such as the National Cholesterol Education Program (NCEP), the American College of Clinical Endocrinologist (ACCE) and the European Group for the Study of Insulin Resistance (EGIR) have published their own definitions [27-28].

However, the consensus group of the International Diabetes Federation (IDF) has proposed a definition of MetS in childhood and adolescence, easily applicable in clinical practice. This definition is based on percentiles and age groups, requires longitudinal studies and highlights the importance of early identification of the specific components of MetS to effectively control the evolution and treatment of children who will develop metabolic and cardiovascular alterations in adult life. The IDF even mentions that the criteria included in this definition cannot diagnose the MetS in minors six years, if it suggests strict follow-up based on family history [26-28].

Criteria	Obesity	Triglycerides	HDL-C	Arterial Hypertension	Glucose	MetS
National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)	Percentile> 90 waist circumference Percentile ≥ 85 of body mass index (BMI) Percentile ≥ 85 of body mass index (BMI)	Children: percentile ≥ 75 Adolescents: ≥ 110mg/dL or percentile> 95	Children: percentile ≤ 25 Teenagers: ≤ 40 mg/dL	Systolic or diastolic blood pressure percentile ≥ 90	Baseline glycemia > 100 mg/dL or postprandial > 140 mg/dL	If the child or young person has at least 3 of these components
International Diabetes Federation (IDF)	Percentile > 90 waist circumference	≥ 150 mg/dL	< 40 mg/dL	> 130 mmHg systolic or 85 mmHg diastolic	Baseline glycemia > 100 mg/dL or postprandial > 140 mg/dL	Abdominal obesity plus two other criteria in adolescents between 10 to 16 years old

Cuban proposal [5].	Percentile > 97 for age and sex	> 110 mg/dL	<40 mg/dL	> 95 percentil (for age and sex)	fasting altered glycemia (6.1 mmol / L)	Three or more of the criteria listed for children and adolescents, (body mass index (BMI), waist-hip ratio (ICC), blood pressure (TA)).
Colombian proposal [29].	Percentile> 90 waist circumference	≥ 110 mg/dL or percentile > 95	Children: percentile ≤ 25 Teenagers: ≤ 40 mg/dL	percentile ≥ 90	Baseline glycemia > 100 mg/dL or postprandial > 140 mg/dL	including ≥3 of the following metabolic abnormalities: WC ≥ 90 cm HDL-c <40 mg/dL triglyceride ≥150 mg/dL; fasting glucose ≥ 100 mg/dL; systolic BP (SBP) ≥ 130 mmHg; and/or diastolic BP (DBP) ≥ 85 mmHg

Table 1: *Comparison of criteria for evaluating MetS in children and adolescents according to NCEP ATP III, IDF.*

*Modificada de Romain Pierlot., *et al*. 2017 [30].

The body mass index (BMI) is the most commonly used measure in clinical practice to determine the degree of obesity in childhood. In several studies performed on children obese, (BMI higher than the percentile 95 for age and sex), there is an evident association between severity of obesity and MetS. However, obesity perse or BMI is not a sufficient marker to identify children at risk of IR and MetS and, as a consequence, cardio metabolic risk. On the other hand, the distribution of visceral fat influences the development of metabolic complications of obesity and, is associated with the development of MetS in childhood and cardiovascular disease in the adult. Circumference of the abdominal waist (CC) is recognized as the best clinical indicator of visceral fat accumulation and, therefore, CC can be a more adequate measure in terms of MS and cardio metabolic risk. For children, in several studies, CC reference values have been described, however, its use is not routine in clinical practice [26,31].

Studies in children with the same degree of obesity have shown that those with higher CC are more likely to have altered cardio metabolic risk factors compared to those with lower CC. In fact, the increase in CC is associated with high blood pressure, increased plasma levels of LDL cholesterol, triglycerides and insulin and decreased HDL cholesterol. The association between CC and this group of cardiovascular risk factors is not only a reflection of a certain degree of obesity, but also seems to have pathophysiological connotations, although the mechanisms involved are not clearly known [6,26].

Although the physical examination and review of BMI and CC measurements is basic, family history should be investigated due to the influence of hereditary factors on the development of the various components of MetS and because several studies have shown that children who do not develop MetS at an early stage are less likely to develop it later.

As mentioned, MetS is defined by elevated plasma triglycerides (TG), blood pressure, fasting glucose and waist circumference, reduced high-density lipoprotein cholesterol (HDL-C). Beyond traditional lipid markers and elevated blood glucose, patients with metabolic syndrome have a substantial residual risk of cardiovascular disease (CVD). On the other hand, chronic low-level inflammation, prevalent in MetS, is associated with a reduction in the antioxidant capacity of HDL. The ability of HDL to perform reverse cholesterol transport, another key atheroprotective function, may also be compromised by factors associated with MetS. [32]. Additionally, it is suggested that preclinical MetS and dyslipidemia in particular are associated with altered variation of myocardial signal intensity [33].

Patients with DM1 have an increased risk of morbidity and mortality from CVD [34-36], however, the underlying mechanisms are only partially understood, and even when the traditional risk factors for these pathologies have been addressed, patients with diabetes have a significant residual risk of CVD [19,36-37].

In clinical studies, high-density lipoprotein cholesterol levels (HDL-C) are inversely associated with coronary heart disease events and mortality [36,38-39]. Despite the total inverse association of HDL-C with CVD risk, almost 40% of men with coronary heart disease have normal HDL-C levels, and very high levels of HDL-C are associated with a higher risk of major coronary events [36,40,41]. Therefore, HDL-C levels alone do not provide a full explanation of the atheroprotective effects of HDL, suggesting that not all HDLs are functionally equivalent, and that the cardio protective nature of HDL is not accurately represented by the circulating levels of HDL-C. Consequently, the focus has shifted to measurements of HDL function, which have produced a better assessment of CVD risk than quantification of HDL-C [42-43]. Heier., *et al*. [36] showed that HDL function, measured by the HDL-apoA-I exchange (HAE) ratio, was reduced in patients with childhood DM1 compared to healthy control subjects. The difference was observed in patients with a mean age of 13.7 years at the beginning of the study, and was still present in a follow-up examination 5 years later. This study highlights that changes in HAE are a sustained effect that occurs early in the onset of DM1. HAE is a key aspect of reverse cholesterol transport, therefore, these results indicate that the reduction in HDL function it may be a mechanism underlying the increased risk of CVD observed in DM1. The loss of HAE may be related to the antioxidant function of HDL, which is also affected by diabetes. The HDL of patients with this disease cannot reverse the inhibitory effect of oxidized LDL on endothelium-dependent vasorelaxation. As a result, reductions in the HAE-apoA-I ratio may be due to the increased inflammation associated with diabetes.

It has been described that there is a specific phenotype of obesity, which is associated with alterations in insulin sensitivity and cardio metabolic complications and characterized by a high proportion of visceral fat and relatively low subcutaneous fat, as for example in the nonalcoholic fatty liver disease (NAFLD) that is currently the most common chronic liver disease in developed countries because of the obesity epidemic. The influence of NAFLD on the development of other metabolic diseases is relevant and epidemiological evidence indicates that NAFLD not only affects the liver but also increases the risk of extrahepatic diseases such as DM2, metabolic syndrome, dyslipidemia, hypertension, cardiovascular or cerebrovascular diseases and chronic kidney disease. Nonalcoholic steatohepatitis (NASH), an advanced type of NAFLD, can aggravate these relationships between organs and lead to poorer outcomes. NAFLD induces insulin resistance and exacerbates chronic systemic inflammation and oxidative stress, which leads to organ dysfunction in extrahepatic tissues. Despite the current evidence, more research is needed to identify the pathophysiological mechanisms and the causal relationship between NAFLD and cardio metabolic and renal diseases, the detection of cardiac, cerebral and renal diseases, as well as for the risk assessment for diabetes. [44,45]

Epidemiological data shows the global prevalence of NAFLD in different populations as follows: United States, 30%, Middle East, 32%, South America, 30%, Asia, 27%, Europe, 24% and Africa, 13%. Wide variations in the prevalence have also been identified among different ethnic groups of these populations and another interesting trend noted is the increasing prevalence of NAFLD among pediatric age groups. Autopsy-based data showed that NAFLD prevalence among children aged 2-19 years to be 9.6% after adjustment for age, sex, race and ethnicity, and up to 38% in obese children [45-47].

The disease starts with fatty liver or hepatic steatosis and may progress to steatohepatitis with hepatic inflammation. Five to twenty percent of patients with fatty liver develop NASH in their clinical course, of which 10-20% develop into higher-grade fibrosis and < 5% progress to full-blown cirrhosis [46,48] The prevalence of NASH may be underestimated, as the diagnosis requires histological confirmation. It is considered that at least 5% of the population may have NASH [44,45,49].

IR is one of the basic pathophysiological mechanisms in the development of MetS and, therefore, it is advisable to measure it in potential risk patients. Hypertension is one of the basic components of MetS, since it has shown a significant relationship between insulin levels and blood pressure. On the other hand, the insulinemia correlates with the future blood pressure that these children will present when they reach adolescence. The most characteristic profile is systolic arterial hypertension in a first phase, accompanied in a later phase of diastolic hypertension. On the other hand, the most frequent altered lipid profile presented by patients with IR and MS is characterized by an increase in triglycerides and a decrease in HDL cholesterol. It is worth mentioning that in all obese adolescents this phenotype does not occur [26].

Colombia is in an intermediate stage of the demographic transition process, the country is experiencing an accelerated aging process, the number of people over 65 over the last 40 years has tripled and the life expectancy at birth has increased to 75.2 years [50]. The profile of morbidity and mortality is characterized by a predominance of chronic non-communicable diseases that for several years have been the main causes of morbidity and mortality: cancers, cardiovascular diseases, metabolic diseases and neurodegenerative diseases appear in the first places at the national level in the burden of disease studies of 1995, 2005 and 2010. The adolescent's eating behavior is influenced by family habits, the greater social bonding with their peers and the growing concern about body image, and on the other hand, by the needs of food energy. The course of obesity from childhood to adulthood and the risk associated with chronic non-communicable diseases, highlight the importance of preventive measures during puberty: as more individuals become obese at an early age, it grows the impact of obesity as a public health problem. This condition is one of the most common nutritional disorders in adolescence and, unlike other disorders that affect health, it has the greatest adverse consequences at the individual, economic and social levels. In the work carried out by Fortich and Gutiérrez [51] it is highlighted that there are social determinants that could influence overweight and obesity such as education, sex, poverty, place of residence, among others.

Childhood Obesity

The Cardioinfantil Foundation, indicated that many of the problems of obesity and overweight begin in pregnancy between 0 to 6 months and in early childhood, According to data provided by the entity, in 2012 there was an increase of 6.7% in children under 5 years of age with obesity problems worldwide.

In Colombia, children under 5 suffer from excess weight, 20.2% are between 1 and 2 years old, and 5.2% are older than 2 years. These problems are associated with a chain that begins with mothers, finding that factors such as malnutrition (12.6%), overweight (24.8%), obesity (9.8%) and anemia (18.8) trigger in low weight, intrauterine growth retardation and high birth weight in newborn children. Similarly, the lack of breastfeeding leads to problems for the child, such as obesity, insulin resistance, diabetes mellitus type 2, hypertension and dyslipidemia, which are also reflected later in youth and adulthood [50].

Relatively recent data suggest that about half of adults in LA are overweight or obese, compared to 33.9% reported a decade earlier [52-54]. Adolescents worldwide are not immune to this trend. In fact, WHO is calling childhood obesity "one of the most serious public health challenges of the 21st century" Countries experiencing rapid demographic and nutritional transitions due to the evolution of the economic climate, like many Latin American countries, are among the most vulnerable [52-58]. A study of adolescents from low-middle-income countries (LMICs) found that LA and the Caribbean had the highest regional prevalence of overweight in both rural and urban areas [59].

The lifestyle of the university population has changed considerably in the last 20 years due to a rapid improvement in socioeconomic status [60,61]. These changes, in addition to the adoption of a Western lifestyle and diet, have led to an increase in the prevalence of overweight and obesity among Colombians, particularly among university students [62]. Other studies have reported MetS in younger populations, but use a much wider age range [63] or include non-university students [64-66]. In addition, in all studies it has been a challenge to clearly define the "young adult" age group. In cross-sectional studies previously reported, the prevalence of MetS in adolescents included ages of 12-18 years [63] or 10-19 years [67]. Having an international definition for the "young adult" age group would be useful for future data comparisons [29].

In this study, it was shown that the prevalence of MetS of 6%, which is an intermediate value compared to those reported in local and international studies, ranging from 2% to 13% (29-38). In other studies [29,68] it was reported a prevalence of 6.8% in university students with characteristics similar to those found in this study. Ford., *et al.* [69] conducted a cross-sectional study with adults aged

18-30 years in the United States and reported a similar prevalence of MetS of 6.7%, using the definition of the National Program of Education on Cholesterol-Adult Treatment Panel III of the United States. United.

The rates found in university contexts reported were higher than those found by Huang., *et al*. [70]. in 163 students aged 18-24 years in Kansas, United States, (0.6%); de Freitas., *et al*. [71] in 702 Brazilian university students (1.7%); Fernandes., *et al*. [72] in 189 students aged 18-24 years (3.7%); Yen., *et al*. [73]. in 8226 students with an average age of 19.2 ± 2.3 years (4.6%); and Burke., *et al*. [74] in 1701 students aged 18-24 years, who enrolled in an introductory nutrition course and met the age requirements of the Young Adult Health Risk Screening Initiative at the University of New Hampshire (4.9 %). On the other hand, the rates described by Martínez-Torres., *et al*. [29] were lower than those found by Ruano., *et al*. [75] and Mattsson., *et al*. [76] in 796 Spanish students between 17 and 25 years old (7.5%), in 2182 healthy young adults (1007 men and 175 women) between 24 and 39 years old (13%), respectively.

These results suggest that the prevalence of MetS could vary between studies according to the MetS group used, the design method and the target population. In this study, the criteria of the International Diabetes Federation (IDF) and the American Heart Association (AHA) and the joint declaration of the National Heart, Lung and Blood Institute (NHLBI) were used as an international attempt to harmonize the definition of MetS. It is worth mentioning that central obesity is not a mandatory component of this definition and is ethnically specific.

Conclusions

The present mini review shows that the prevalence of MetS and its components in various countries is variable, presenting in some of them prevalences small, and in other highs. This variability is possibly due to the difference in eating habits and care of the health of each country, but also of the diversity of detection criteria used and lack of consensus among them for the diagnosis and cut points for the MetS components.

In summary, it is shown that the prevalence of MetS and its components is relevant in children and adolescents and that dyslipidemia, central obesity and high blood pressure levels are the most frequent components of MetS. It is recommended that each country incorporate strategies to improve nutrition and physical activities, in order to counteract this health problem in young people.

Acknowledgments

The author wish to acknowledge the financial support provided by the National Institute of Health of Colombia.

References

1. García García E. "Obesidad y síndrome metabólico en pediatría". En AEPap ed. Curso de Actualización Pediatría 3.0 (2015): 71-84.
2. Grundy SM., *et al*. "Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Executive summary". *Cardiology in Review* 13.6 (2005): 322-327.
3. Alberti KG., *et al*. "Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; world heart federation; international atherosclerosis society; and International Association for the Study of obesity". *Circulation* 120.16 (2009): 1640–1645.
4. He X., *et al*. "Prevalence and clinical profile of metabolic syndrome in longevity: study from Guangxi Zhuang Autonomous Region, China". *BMC Geriatrics* 17.1 (2017): 169.
5. Alpízar Caballero L. "El síndrome metabólico en niños y adolescentes". *Revista Cubana de Medicina Militar* 42.4 (2013): 464-471.
6. Weiss R., *et al*. "Obesity and the Metabolic Syndrome in Children and Adolescents". *The New England Journal of Medicine* 350.23 (2004): 2362-2374.
7. Kaldmäe M., *et al*. "Prevalence of cardiovascular disease risk factors in Tallinn, Estonia". *Medicina (Kaunas)* 53.4 (2017): 268-276.
8. Masanovic M., *et al*. "The geographic patterns of the exceptional longevity in Croatia". *Collegium Antropologicum* 33.S1 (2009): 147-152.

9. Szewieczek J., *et al*. “Mildly elevated blood pressure is a marker for better health status in polish centenarians”. *Age (Dordr)* 37.1 (2015): 4.
10. Milman S., *et al*. “Phenotypes and genotypes of high density lipoprotein cholesterol in exceptional longevity”. *Current Vascular Pharmacology* 12.5 (2014): 690-697.
11. Barzilai N., *et al*. “Unique lipoprotein phenotype and genotype associated with exceptional longevity”. *JAMA* 290.15 (2003): 2030-2040.
12. Heijmans BT., *et al*. “Lipoprotein particle profiles mark familial and sporadic human longevity”. *PLOS Medicine* 3.12 (2006): e495.
13. Gong YY., *et al*. “Glucose and lipid profile of a long-lived rural Han Chinese population and their families in southwest China”. *Journal of the American Geriatrics Society* 57.3 (2009): 567-568.
14. He YH., *et al*. “Improved lipids, diastolic pressure and kidney function are potential contributors to familial longevity: a study on 60 Chinese centenarian families”. *Scientific Reports* 6 (2016): 21962.
15. Zhang M., *et al*. “Risk of type 2 diabetes mellitus associated with plasma lipid levels: The rural Chinese cohort study”. *Diabetes Research and Clinical Practice* 135 (2017): 150-157.
16. Yeboah K., *et al*. “Metabolic syndrome and parental history of cardiovascular disease in adults in urban Ghana”. *BMC Public Health* 18.1 (2017): 96.
17. Alegría Ezquerra E., *et al*. “Obesidad, síndrome metabólico y diabetes: implicaciones cardiovasculares y actuación terapéutica”. *Revista Española de Cardiología* 61.7 (2008): 752-764.
18. Gunturiz ML and Chaparro PE. “Diabetic Cardiomyopathy: Cause or Consequence of Diabetes Mellitus?” *Cardiology and Cardiovascular Medicine* 1.4 (2017): 155-168.
19. Kim NH., *et al*. “Risk of the Development of Diabetes and Cardiovascular Disease in Metabolically Healthy Obese People: The Korean Genome and Epidemiology Study”. *Medicine (Baltimore)* 95.15 (2016): e3384.
20. Jee SH., *et al*. “Body-mass index and mortality in Korean men and women”. *The New England Journal of Medicine* 355.8 (2006): 779-787.
21. Speiser PW., *et al*. “Obesity Consensus Working Group. Childhood obesity”. *The Journal of Clinical Endocrinology & Metabolism* 90.3 (2005): 1871-1887.
22. Choi KM., *et al*. “Higher mortality in metabolically obese normal-weight people than in metabolically healthy obese subjects in elderly Koreans”. *Clinical Endocrinology (Oxford)* 79.3 (2013): 364-370.
23. Guo SS., *et al*. “Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence”. *The American Journal of Clinical Nutrition* 76.3 (2002): 653-658.
24. Appleton SL., *et al*. “Diabetes and cardiovascular disease outcomes in the metabolically healthy obese phenotype: a cohort study”. *Diabetes Care* 36.8 (2013): 2388-2394.
25. Soriguer F., *et al*. “Metabolically healthy but obese, a matter of time? Findings from the prospective Pizarra study”. *The Journal of Clinical Endocrinology & Metabolism* 98.6 (2013): 2318-2325.
26. Bel Comós J and Murillo Valles M. “Obesidad y síndrome metabólico”. *Protoc diagn ter pediatr* 1 (2011): 228-235.
27. D’Adamo E., *et al*. “Metabolic Syndrome in Pediatrics: Old Concepts Revised, New Concepts Discussed”. *Endocrinology Metabolism Clinics of North America* 38.3 (2009): 549-563.
28. Zimmet P., *et al*. “The metabolic syndrome in children and adolescents–an IDF consensus report”. *Pediatric Diabetes* 8.5 (2007): 299-306.
29. Martínez Torres J., *et al*. “A Cross-Sectional Study of the Prevalence of Metabolic Syndrome and Associated Factors in Colombian Collegiate Students: The FUPRECOL-Adults Study”. *International Journal of Environmental Research and Public Health* 14.3 (2017): 233.
30. Romain P., *et al*. “Prevalencia de síndrome metabólico en niños y adolescentes de américa”. *Revista Especializada en Ciencias Químico-Biológicas* 20.1 (2017): 40-44.
31. Berenson GS., *et al*. “Association between multiple cardiovascular risk factor and atherosclerosis in children and young adults: the Bogalusa Heart Study”. *The New England Journal of Medicine* 338.23 (1998): 1650-1656.

32. Borja MS., *et al*. "Apolipoprotein A-I exchange is impaired in metabolic syndrome patients asymptomatic for diabetes and cardiovascular disease". *PLoS ONE* 12.8 (2017): e0182217.
33. Magge SN., *et al*. "The Metabolic Syndrome in Children and Adolescents: Shifting the Focus to Cardiometabolic Risk Factor Clustering". Pediatrics (2017): e20171603.
34. Soedamah-Muthu SS., *et al*. "High risk of cardiovascular disease in patients with type 1 diabetes in the UK: a cohort study using the general practice research database". Diabetes Care 29.4 (2006): 798-804.
35. Laing SP., *et al*. "Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes". Diabetologia 46.6 (2003): 760-765.
36. Heier M., *et al*. "Reduced HDL function in children and young adults with type 1 diabetes". Cardiovascular Diabetology 16.1 (2017): 85.
37. Hero C., *et al*. "Association between use of lipid-lowering therapy and cardiovascular diseases and death in individuals with type 1 diabetes". Diabetes Care 39.6 (2016): 996-1003.
38. Gordon T., *et al*. "High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study". American Journal of Medicine 62.5 (1977): 707-714.
39. Gordon DJ., *et al*. "High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies". Circulation 79.1 (1989): 8-15.
40. Asztalos BF., *et al*. "High-density lipoprotein subpopulation profile and coronary heart disease prevalence in male participants of the Framingham Offspring Study". Arteriosclerosis, Thrombosis, and Vascular Biology 24.11 (2004): 2181-2187.
41. Van der Steeg., *et al*. "High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A–I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies". Journal of the American College of Cardiology 51.6 (2008): 634-642.
42. Oda MN. "High-density lipoprotein cholesterol: origins and the path ahead". *Current Opinion in Endocrinology, Diabetes and Obesity* 22.2 (2015): 133-141.
43. Mody P., *et al*. "Beyond coronary calcification, family history, and C-reactive protein: cholesterol efflux capacity and cardiovascular risk prediction". *Journal of the American College of Cardiology* 67.21 (2016): 2480-2487.
44. Han E., *et al*. "Non-Alcoholic Fatty Liver Disease: The Emerging Burden in Cardiometabolic and Renal Diseases". *Diabetes and Metabolism Journal* 41.6 (2017): 430-437.
45. Pappachan JM., *et al*. "Non-alcoholic Fatty Liver Disease: A Clinical Update". *Journal of clinical and translational hepatology* 5.4 (2017): 384-393.
46. Carr RM., *et al*. "Nonalcoholic fatty liver disease: pathophysiology and management". *Gastroenterology Clinics of North America* 45.4 (2016): 639-652.
47. Schwimmer JB., *et al*. "Histopathology of pediatric nonalcoholic fatty liver disease". *Hepatology* 42.3 (2005): 641-649.
48. Bataller R., *et al*. "Fibrosis in alcoholic and nonalcoholic steatohepatitis". *Best Practice & Research: Clinical Gastroenterology* 25.2 (2011): 231-244.
49. Adams L. "Transient elastography in nonalcoholic fatty liver disease: making sense of echoes". *Hepatology* 51.2 (2010): 370-372.
50. www.minsalud.gov.co/salud/paginas/indicadoresbasicossp.asp. Acceso mayo 15 de 2017
51. Fortich R and Gutiérrez J. "Los determinantes de la obesidad en Colombia". *Economía & Región* 5.2 (2011): 155-182.
52. Casapulla SL., *et al*. "Cardiometabolic risk factors, metabolic syndrome and pre-diabetes in adolescents in the Sierra region of Ecuador". *Diabetology & Metabolic Syndrome* 9 (2017): 24.
53. Aballay LR., *et al*. "Overweight and obesity: a review of their relationship to metabolic syndrome, cardiovascular disease, and cancer in South America". *Nutrition Reviews* 71.3 (2013): 168-179.
54. Popkin BM and Slining MM. "New dynamics in global obesity facing low- and middle-income countries". *Obesity Reviews* 14.2 (2013): 11-20.
55. World Health Organization. "Global strategy on diet, physical activity, and health: childhood overweight and obesity". *Geneva: World Health Organization* (2004):

56. Montero J. "Latin American experiences in the prevention of obesity". *West Indian Medical Journal* 51 (2002): 37.
57. Whiting DR., *et al*. "IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030". *Diabetes Research and Clinical Practice* 94.3 (2011): 311-321.
58. Azad MB., *et al*. "Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies". *CMAJ* 189.28 (2017): E929-E939.
59. Jaacks LM., *et al*. "Recent trends in the prevalence of under- and overweight among adolescent girls in low- and middle-income countries: adolescent under/overweight in LMICs". *Pediatric Obesity* 10.6 (2015): 428-435.
60. Ramírez-Vélez R., *et al*. "A cross-sectional study of Colombian University students' self-perceived lifestyle". *SpringerPlus* 4 (2015): 289.
61. Al Dhaheri AS., *et al*. "A Cross-Sectional Study of the Prevalence of Metabolic Syndrome among Young Female Emirati Adults". *PLoS ONE* 11.7 (2016): e0159378.
62. Fonseca-Camacho DF., *et al*. "A better self-perception of physical fitness is associated with lower prevalence of metabolic syndrome and its components among university students". *Nutricion Hospitalaria* 31.3 (2014): 1254-1263.
63. Ramírez-Vélez R., *et al*. "Metabolic Syndrome and Associated Factors in a Population-Based Sample of Schoolchildren in Colombia: The FUPRECOL Study". *Metabolic Syndrome and Related Disorders* 14.9 (2016): 455-462.
64. Daviglus ML., *et al*. "Cardiovascular disease risk factors in the Hispanic/Latino population: Lessons from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)". *Progress in Cardiovascular Diseases* 57.3 (2014): 230-236.
65. Llabre MM., *et al*. "Do all components of the metabolic syndrome cluster together in U.S. Hispanics/Latinos? Results from the Hispanic Community Health study/Study of Latinos". *Annals of Epidemiology* 25.7 (2015): 480-485.
66. Zheng R., *et al*. "Prevalence and Determinants of Metabolic Health in Subjects with Obesity in Chinese Population". *International Journal of Environmental Research and Public Health* 12.11 (2015): 13662-13677.
67. Ramírez-Vélez R., *et al*. "Association between adiposity and cardiovascular risk factors in infants pre-pubertal". *Endocrinologia Y Nutricion 5*8.9 (2011): 457-463.
68. Dalleck L and Kjelland E. "The prevalence of metabolic syndrome and metabolic syndrome risk factors in college-aged students". *American Journal of Health Promotion* 27.1 (2012): 37-42.
69. Ford E., *et al*. "Increasing prevalence of the metabolic syndrome among U.S. adults". *Diabetes Care* 27.10 (2004): 2444-2449.
70. Huang TTK., *et al*. "Overweight and components of the metabolic syndrome in college students". *Diabetes Care* 27.12 (2004): 3000-3001.
71. De Freitas RJ., *et al*. "Prevalence of the metabolic syndrome and its individual components in Brazilian college students". *Journal of Clinical Nursing* 22.9-10 (2013): 1291-1298.
72. Fernandes J and Lofgren I. "Prevalence of metabolic syndrome and individual criteria in college students". *Journal of American College Health* 59.4 (2011): 313-321.
73. Yen S., *et al*. "Obesity and hepatitis B infection are associated with increased risk of metabolic syndrome in university freshmen". *International Journal of Obesity* 32.3 (2008): 474-480.
74. Burke J., *et al*. "The University of New Hampshire's Young Adult Health Risk Screening Initiative". *Journal of the American Dietetic Association* 109.10 (2009): 1751-1758.
75. Ruano-Nieto C., *et al*. "Prevalence of metabolic syndrome and associated risk factors in ecuadorian university students". *Nutricion Hospitalaria* 31.4 (2015): 1474-1481.
76. Mattsson N., *et al*. "The prevalence of the metabolic syndrome in young adults. The Cardiovascular Risk in Young Finns Study". *Journal of Internal Medicine* 261.2 (2007): 159-169.