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DYSLIPIDEMIA AMONG 13-YEAR-OLD ADOLESCENTS:

THE EPITEEN COHORT STUDY

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ABSTRACT

Dyslipidemia is a major contributing risk factor for atherosclerosis and cardiovascular disease. Despite clinical manifestations occurring in adulthood, atherosclerosis begins in the first decades of life, which reinforces the importance of primary prevention of atherosclerotic cardiovascular disease in children. The American Heart Association and the American Academy of Paediatrics recognize this and recommended lipid screening of high risk children no later than 10 years of age.

There are few pediatric studies concerning atherosclerosis and cardiovascular diseases worldwide, and specially in Portugal. Portugal presents a different pattern of cardiovascular disease, with higher stroke mortality than in most European countries, and data from our cohort of 13-year-old adolescents could help to understand if this difference may be explained by a different pathway from that usually found in other countries. Moreover, most previous studies that have focused on determinants of dyslipidemia in children and adolescents aggregated a wide variety of ages analysed within one category, and our 13-year-old adolescent study tries to focus on a specific age during adolescence, minimizing possible confounding factors that this aggregation could hide. As up to forty per cent of pre-pubertal cholesterol levels do not persist after sexual maturation, this age could be considered for tracing dyslipidemia in non-high risk children.

Aim: To access prevalence of dyslipidemia and to identify associated characteristics in urban 13-year-old adolescents.

Methods: Participants were 13-year-old urban adolescents, accessed at the baseline evaluation of a population-based cohort. All public and private schools with 13-year-old students in Porto were approached. Blood samples of 1388 adolescents were collected to obtain lipid serum values. Associations between dyslipidemia or each of its components and the characteristics of adolescents were evaluated by odds ratio (OR) and 95% confidence interval (95%CI) calculated using unconditional logistic regression. Self-administered questionnaires provided information of parental education and BMI, familiar history of hypercholesterolemia or diabetes, sports practice and age at menarche in girls. A physical examination was performed, including weight, height measurements and blood pressure.

Results: Abnormal total- and LDL-cholesterol levels were associated with parents' history of hypercholesterolemia. Overall, dyslipidemia was present in 24.5% of the adolescents (23.4% in girls and 25.6% in boys, p=0.375), and significant association was found in relation with parent's history of hypercholesterolemia (OR=1.32 (CI95% 1,00-1,76)) and with adolescents' BMI (OR=1.38 (CI95% 1,00-1,92)) for overweight and 3.56 (2.48-5.12) for obese). Boys had a higher prevalence of low HDL-cholesterolemia (14.0% vs. 9.1%, p=0.005). No statistical significant differences were found between adolescents with and without blood sample. No significant differences in serum lipids were noted according to parents' overweight, parents' history of diabetes, adolescent sports' practice or, in girls, to the age at menarche.

Conclusion: Prevalence of dyslipidemia was high. Family history of dyslipidemia and BMI were the main determinants of dyslipidemia at this age. In 13-year-old girls, lipids were not influenced by the age at menarche.

RESUMO

A dislipidemia é um factor de risco major para aterosclerose e doença cardiovascular. Apesar das manifestações clínicas ocorrerem na idade adulta, a aterosclerose inicia-se nas primeiras décadas de vida, e daí a importância da prevenção primária da doença cardiovascular aterosclerótica na criança. As Academias Americanas de Cardiologia e de Pediatria reconhecem a importância destes dados e recomendam que o rastreio de dislipidemias a crianças de alto risco seja efectuado até aos 10 anos de idade.

Existem poucos estudos que abordem a arteriosclerose e a doença cardiovascular em pediatria a nível mundial e especialmente em Portugal. Portugal, em relação a outros países da Europa, apresenta uma diferente distribuição de doença cardiovascular, com uma mortalidade por acidente vascular cerebral superior à maioria dos países europeus, e por isso os dados da nossa coorte de adolescentes de 13 anos de idade poderiam ajudar a entender se esta diferença poderia ser explicada por uma via diferente da usualmente encontrada em outros países. Adicionalmente, a maioria dos estudos anteriores que focam os determinantes de dislipidemia em crianças e adolescentes agregam e analisam habitualmente diferentes idades numa mesma categoria, e o nosso estudo em adolescentes de 13 anos de idade tenta focar uma idade específica durante a adolescência, minimizando possíveis factores confundidores provenientes da agregação de idades. Dado que até 40% dos valores de hipercolesterolemia podem não persistir após a puberdade, esta poderia ser uma idade adequada para rastrear dislipidemia em crianças que não sejam de alto risco.

Objectivo: Determinar a prevalência de dislipidemia e identificar características associadas, em adolescentes de 13 anos de idade provenientes de um meio urbano.

Métodos: Participaram no estudo os adolescentes de 13 anos de idade membros da coorte de Investigação Epidemiológica em Saúde EPITeen da cidade do Porto, avaliados no inicio da investigação. No recrutamento foram abordadas todas as escolas públicas e privadas do Porto que tinham estudantes com 13 anos de idade. Um total de 1388 adolescentes colheu sangue para determinação de valores séricos de lipidos. Foram avaliadas as associações entre dislipidemia ou cada um dos seus componentes e as características dos adolescentes através da determinação do Odds Ratio e dos seus intervalos de confiança, calculados por regressão logística. Efectuaram-se questionários onde foram avaliados a educação dos pais e o seu IMC, história familiar de hipercolesterolemia ou diabetes, prática de desporto e idade da menarca nas raparigas. Foi ainda efectuado um exame físico que incluiu peso, estatura e pressão arterial.

Resultados: Níveis elevados de colesterol total e colesterol LDL associaram-se a história familiar de hipercolesterolemia. Globalmente, a dislipidemia foi encontrada em 24.5% dos adolescentes (23.4% nas raparigas e 25.6% nos rapazes, p=0.375) e foi encontrada uma associação significativa com história familiar de hipercolesterolemia (OR=1.32 (CI95% 1,00-1,76)) e com o IMC do adolescente (OR=1.38 (CI95% 1,00-1,92) para excesso de peso e 3.56 (2.48-5.12) para obesidade). Os rapazes tiveram uma maior prevalência de HDL-colesterol baixo (14.0% vs. 9.1%, p=0.005). Não houve diferenças significativas entre os adolescentes que colheram e os que não colheram sangue para estudo analítico. Não foram encontradas também diferenças significativas nos lipidos séricos tendo em conta excesso de peso dos pais, história de diabetes nos pais, prática de desporto por parte do adolescente ou, nas raparigas, a idade da menarca.

Conclusão: A prevalência de dislipidemia foi elevada. A história familiar de dislipidemia e o IMC foram os principais determinantes de dislipidemia nesta idade. Nas raparigas de 13 anos, os lipidos não foram influenciados pela idade da menarca.

BACKGROUND

THE BURDEN OF CARDIOVASCULAR DISEASE

Each year cardiovascular disease (CVD) causes 17.1 million deaths all over the world and over 4.3 million deaths in Europe(1). This represents the world largest killer, and 48% of all causes of deaths in Europe(2). Almost half of all deaths from CVD are from coronary heart disease (CHD) and nearly a third is from stroke. Death rates from these diseases are generally higher in Central and Eastern Europe than in Northern, Southern and Western Europe. Besides, CVD mortality, incidence and case fatality are falling in most Northern, Southern and Western European Countries but either not falling as fast or rising in Central and Eastern European countries(2). Portugal in particular, despite having a low CVD death rate, has a relatively higher stroke mortality rate than that in other South European countries(2-3), and thus risk factors for CVD in Portugal might be somewhat different than in other countries.

In Portugal, cardiovascular disease is the main cause of death, increasing from 26.4% in 1960 to 38.7% in 2000(2). Portugal has the highest stroke mortality rate in Western Europe, and although reducing dramatically over the past two decades, it remains higher than that for most European countries. In contrast, coronary heart disease mortality is low and similar to Spain and Italy, also countries with historically low coronary heart disease rates(2).

Most studies in Portugal concern prevalence of risk factors for atherosclerosis and cardiovascular diseases, like hypertension, diabetes, smoking, obesity and metabolic syndrome, and most of these are in adults. Prevalence of some of these risk factors is

unknown. Risk factors for cardiovascular diseases such as hypertension, smoking, hypercholesterolemia and sedentarism are highly prevalent(3-9).

Life expectancy at birth for both sexes has been improving all over the world in the last decades. In Europe, when compared to the level in 1950, this represented an increase in life expectancy of over 15 years in southern Europe, 11 years in Western Europe and about 9 years in northern Europe. In Eastern Europe, there was a smaller increase of about 4 years(10). Over the next 25 years, as population age in middle and low-income countries increases, the proportion of deaths due to noncommunicable diseases will rise significantly, as it is predicted. Cardiovascular disease will rise from 17.1 million deaths in the world in 2004 to 23.4 million in 2030, and by then, it is predicted that the four leading causes of death in the world in 2030 will be ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease and lower respiratory infections(10). In general, it is expected for Europe and for the world an increase burden of these diseases.

At the same time morbidity is also increasing, as longevity increases and medical care improves. Cardiovascular disease is a major cause of disability and lost productivity in adults(11). It turns out that no other life-threatening disease is as prevalent or expensive to society, and persons with CVD are likely to die from their disease. The aging population, obesity epidemic, underuse of prevention strategies, and suboptimal control of risk factors could exacerbate the future CVD burden.

Taking into account all those factors, and regarding that the main cause of cardiovascular disease is atherosclerosis, that is a continuous process that can be prevented, acknowledgement and prevention of its modifiable risk factors could contribute to a significant decrease in cardiovascular events.

ATHEROSCLEROSIS

Arteriosclerosis refers to the presence of atherosclerotic changes within the walls of minor and medium arteries, which causes impairment or obstruction of normal blood flow with resultant ischemia(12). The distribution of lipid and connective tissue in the atherosclerotic lesions determines whether they are stable or at risk of rupture, thrombosis, and clinical sequelae.

This is a progressive process that generally begins in childhood and manifests clinically in mid-to-late adulthood(12-16).

ATHEROSCLEROSIS FIRST STEPS/ ETIOPATHOGENY

The precursors of atherosclerosis are arranged in a temporal sequence of three characteristic lesion types (I, II, III). They are silent and do not lead directly to complications. The initial lesion in atherosclerosis involves the intima of the artery and begins in childhood with the development of fatty streaks. Advanced lesions involve disorganization of the intima and deformity of the artery and are either overtly clinical or they predispose to the complications that cause ischemic episodes(17).

Type I lesions represent the very initial changes and are recognized as an increase in the number of intimal macrophages and the appearance of macrophages filled with lipid droplets (foam cells).

Type II lesions include the fatty streak lesion, the first grossly visible lesion, and are characterized by layers of macrophage foam cells and lipid droplets within intimal smooth muscle cells and minimal coarse-grained particles and heterogeneous droplets of extracellular lipid.

Type III (intermediate) lesions are the morphological and chemical bridge between type II and advanced lesions (type IV-VIII). They appear in some adaptive intimal thickenings (progression-prone locations) in young adults and are characterized by pools of extracellular lipid in addition to all the components of type II lesions.

Types I and II are generally the only lesion types found in children. For most children, atherosclerotic vascular changes are minor and can be minimized or even prevented with adherence to a healthy lifestyle. On the other hand, this process may be accelerated because of the presence of risk factors (eg, obesity, hypertension) and/or specific diseases that are associated with premature CVD (eg, diabetes, Kawasaki disease)[18].

It is the evidence that atherosclerotic lesions begin early in life and that they can be prevented or postponed by changing risk factors that supports lifestyle modification in youth to prevent development of the initial lesions and the subsequent progression to advanced lesions and delay of coronary heart disease.

RISK FACTORS FOR ATHEROSCLEROSIS

A variety of factors, often acting in concert, are associated with an increased risk for atherosclerose plaques in coronary arteries and other arterial vessels(19). This set of risk factors comprises modifiable and non-modifiable risk factors.

Non-modifiable risk factors are independent factors that cannot be changed, although awareness of these factors is important for prevention.

Modifiable risk factors are partially responsible for interregional variation and susceptible of change through specific preventive measures. Controlling modifiable risk factors can often lessen genetic influences and prevent atherosclerosis, particularly in the youngest.

Non-modifiable risk factors

Among non-modifiable risk factors age, sex and family history are the most important determinants of atherosclerosis and cardiovascular disease.

1- Age

It is known that the risk of coronary heart disease is higher in men older than 45 years and in women older than 55 years-old. Also, the average annual rates of first

major cardiovascular events rise from three per 1,000 men at ages 35–44 to 74 per 1,000 at ages 85–94. For women, comparable rates occur 10 years later in life(20). Although this data represents that most cases of atherosclerotic vascular disease become clinically apparent in patients aged 40 and older, the process behind those diseases, the artherosclerosis, begins early in life(21).

2- Male sex

In developed countries, cardiovascular disease is the main cause of death in both genders, but in men this happens much earlier than in women(20, 22). Women seem to be protected from atherosclerotic disease before menopause, and the main hypothesis for lower cardiovascular disease is that oestrogens would protect women from atherosclerosis. It is known that a lower level of HDL and a higher level of LDL and total cholesterol, or also a higher level of triglycerides, contribute to acceleration of atherosclerosis. So, the mechanism proposed to explain the reduction in CVD is the beneficial effects of oestrogens on lipids and lipoproteins, particularly increasing high-density-lipoprotein cholesterol, and decreasing low-density lipoprotein-cholesterol concentrations(23). After menopause, although HDL-C doesn't significantly change in women, and is usually superior than in men, total cholesterol and LDL-C become more elevated and TG also rise, reaching similar values to men after the age of 70(24). At age 80 both men and women have similar values of HDL-C, LDL-C, total-C and TG, which may explain why the gap with the occurrence of cardiovascular diseases narrows with advancing age(25).

Regarding possible effects of oestrogens, there were also noted reductions in fibrinogen, fasting glucose and insulin levels, and beneficial effects on arterial walls(26-27).

At this time, however, controversy exists concerning oestrogen benefits on cardiovascular disease in literature(28). Women with cardiovascular disease have

more complications and higher mortality than men with the same age. Cardiovascular diseases also do not seem to be related with oestrogen levels after menopause. Oral anticonceptives raise the risk of atherosclerosis and cardiovascular diseases in women, especially in those older than 35 years who smoke. They also raise LDL-C, and TG when there is already hypertrigliceridemia. Transdermic oestrogens, on the other way, and according with physiologic oestrogen, decrease triglycerides(29).

3- Family history of early cardiovascular disease

Family history may explain why one person with certain risk factors will have signs of atherosclerosis at an early age, and another one, with apparently the same risk factors, will not have it. Family history is a significant independent risk factor for atherosclerosis and coronary heart disease, particularly among younger individuals with a family history of premature disease(30). Although usually a family history is collected as one total risk factor, it is known that different family histories correspond to different risk factors. A history of paternal myocardial infarction at an age <60 years was associated with a greater risk of cardiovascular disease than infarction at a later age; in comparison, any maternal history of infarction was associated with a greater risk(31). Compared to no parental history of an myocardial infarction, a maternal history, a paternal history, and both maternal and paternal history was associated with a relative risk of cardiovascular disease of 1.71, 1.40, and 1.85 in men and 1.46, 1.15, and 2.05 in women(31).

Modifiable risk factors

Acknowledgment of modifiable risk factors is of major importance, as its prevention actually reduces cardiovascular morbidity and mortality. In addition, as these risk factors are

common to other pathologies, a significative health benefit is expected with cardiovascular modifiable risk factors awareness and prevention.

Most studies associating risk factors for atherosclerosis and cardiovascular disease were conducted in adults. As atherosclerosis begins early in lifetime, and most of these modifiable risk factors and behaviours also begin in childhood, more attention must be paid to risk factors early in life.

Despite some of the risk factors like obesity, diabetes, high blood pressure and dyslipidemia having a non negligible and non modifiable genetic component, the potential to modify these is higher than the expected for non modifiable components.

1- Smoking

Tobacco seems to be the most important risk factor for myocardial infarction events among young individuals[32-34]. According to the World Health Organization (WHO), about 150 million adolescents use tobacco and it is estimated that about 75 million of them will die from tobacco-related diseases later in life[20]. Active and passive smokers are exposed to a wide range of substances with a potential impact in atherogenesis.

It is expected that the impact of smoking on cardiovascular disease will reduce as this has been declining in many European countries. However, as part of the effect is mediated by the effect on atherosclerosis, which means that it is an effect over time, this impact is gradual and takes time. Aditionally, the decline of smoking seems to be slowing[2]. Portugal in particular seems to be on a earlier stage of tobacco dynamic epidemiology, between stage 2 and 3 of tobacco epidemiology evolution, with a high prevalence of tobacco smokers and the prevalence of smoking women still increasing, whilst most North European countries and USA have already reached the fourth stage with prevalence starting to decline [8]. So, the benefits from the expected

reductions on smoking will only appear in several years or decades, particularly if preventive measures are not taken to accelerate the pattern of reduction.

2 – Alcohol

It seems that the relationship between alcohol use and atherosclerotic vascular disease follows the U- or J-shaped pattern seen in studies of alcohol and cardiovascular morbidity and mortality(35-36). A possibility for the benefit of low consumption of wine is that wine would decrease atherosclerotic cardiovascular disease for the potential anti-oxidant effect of some of its components, although it is not proven yet that anti-oxidants benefit atherosclerosis. One best known effect of the light to moderate alcohol intake is to increase circulating levels of HDL-C by 12% average, and another to reduce platelet aggregation.

Despite these possible protective effects, adverse effects are better known. Heavy acute loads of alcohol seem to relate to enhanced progression of carotid atherosclerosis, independent of the total average level of alcohol consumption. Different mechanisms may explain this relation. Like any other source of carbohydrates, alcohol can increase plasma triglyceride levels and VLDL-C. In patients with underlying hypertriglyceridemia elevations of triglycerides can be marked.

Daily intake of more than moderate amounts of alcoholic beverages is also a clear risk factor for the development of hypertension. Additionally, alcoholic beverages can serve as source of excess calories which may contribute to a higher risk of overwheight. Alcohol consumption should never be considered as a preventive measure, particularly in teenagers and young adults, as automobile accidents, trauma, and suicide are leading causes of mortality in this age group, and use of alcohol can contribute to their incidence.

3 - Diet

A number of dietary factors, such as consumption of fresh fruits, vegetables, fiber and fish differ between European populations and can be readily associated with reduced coronary heart disease.

Mediterranean diets and some of their components like fish, olive oil, fruit and vegetables have showed effects related to atherosclerosis that support a possible protective effect on the development of cardiovascular disease.

The role of fruits and vegetables may be mediated by their flavonoids and anti-oxidants, which have been associated with lower markers of inflammation and oxidative stress in adults and seem to be already present by early adolescence[37].

Fish-oil feeding experiments in humans have shown many potential anti-atherogenic effects, namely a lowering of plasma triglycerides concentration and a decrease in platelet aggregation[38].

Intake of N-3-fatty –acids is frequently presented as the responsible for the potential to ameliorate the atherosclerotic process itself and decrease morbility and mortality from coronary heart disease. Nevertheless, until now their benefits remain clear only as secondary prevention.

Although the mechanisms for the protective effect are still unclear, and might result from a set of different factors, the benefits from a diet rich in fruits and vegetables, whole grains, low-fat or non fat dairy products, beans, fish, and lean proteins are clear[39]. The diet that may prevent atherosclerosis shouldn't also have excessive carbohydrates, particularly "refined" carbohydrates (white rice, pasta, bread, desserts), which raise blood sugar and are low in fiber.

The fact that dietary patterns across Europe are now converging, improving in Northern and Western European countries but deteriorating in Southern, Central and Eastern European countries, is not good for the last countries.

4- Physical activity and Sedentarism

Exercise of even moderate degree has a protective effect against coronary heart disease and all-cause mortality(40-41). There is a close relationship between physical inactivity and other atherosclerosis determinants, as obesity, smoking and other unhealthy lifestyles that tend to be present in some individuals. Exercise may have a variety of beneficial effects including an elevation in serum HDL-cholesterol, a reduction in blood pressure, less insulin resistance, and weight loss(42-43), all of them described as potential risk factors for atherosclerosis. Lower physical activity levels are associated with worse arterial stiffness from adolescence to adulthood. Nevertheless, these associations were not uniform throughout the arterial tree, being stronger and independent of other risk factors in the muscular (brachial and femoral) arteries, but dependending on and possibly mediated by concomitant changes in HDL cholesterol and body weight in the elastic carotid artery(44). Therefore, increasing physical activity levels may contribute to a reduction in mortality from cardiovascular disease related with atherosclerosis, through decreasing arterial stiffness.

Sedentarism is highly prevalent worldwide, and in European Union it is more prevalent in the Mediterranean countries(45). It is already prevalent and increasing in adolescence, especially among girls, and is also a major concern in adults, making this risk factor particularly important in this age group.

In the 1998/99 National Health Inquiry, Portugal was considered the most sedentary country in all European Union – in this country, people with more than 15 year-old usually spend their spare time reading, watching tv and doing other sedentary activities(7). In the 2005 National Heath Inquiry, 61% of the Portuguese men and women were still spending their time sitting for more than 3 hours a day(46).

5- Obesity

Obesity is one of the major health problems in industrialized countries. Overweight among children and adolescents has dramatically increased during the last decades(47-48).

In addition, obesity in adolescence tends to persist into adulthood, and high BMI in adolescence seems to predict both adult obesity morbidity and mortality(49). High BMI in children and adolescents may also have immediate consequences such as elevated lipid concentrations and blood pressure.

Obesity itself is an important risk factor for atherosclerosis and cardiovascular disease, but it is especially harmful when associated with other commonly associated risk factors like hypertension, diabetes and dyslipidemias(50-52). Obesity or weight gain promotes or aggravates all this atherogenic risk factors, and most researchers agree that obesity is an important modulator of the metabolic syndrome, which is a clustering of cardiovascular risk factors associated with insulin resistance(53).

The predominant role of the adipose tissue is the storage of lipid energy. In obesity, basal rates of adipose tissue free fatty acids turnover are increased, and the inhibition of lipolysis by insulin is diminished. This results in higher release of free fatty acids into the peripheral circulation and increased available of free fatty acids to various tissues, which is thought to underlie many components of the insulin resistance syndrome. Obesity can also induce a chronic inflammatory state that may worse atherosclerotic disease(54).

Obesity may play an increasing role in disease ocurrence in Portugal, and was strongly related to hypertension and hypertrigliceridemia in both genders. In 2003, Costa J et al found an incidence of 559 new cases of dyslipidemia per 100000 inhabitants, with a gradual increase from 15 years-old onwards(5).

6- High blood pressure

Although systemic hypertension is more prevalent in adults, high blood pressure in childhood and adolescence is associated with elevated blood pressure in the future. This represents the early stages of primary hypertension in adulthood. Primary hypertension in childhood usually occurs in overweight children with family history of hypertension and cardiovascular disease.

In Espiga Macedo et al study (PAP study), 42.1% of the Portuguese population aged 18-90 years had hypertension, with a high percentage of hypertensives unaware of the fact and just 11.2% of those treated having their blood pressure controlled. This is a high prevalence of hypertension that could justify the relative high percentage of stroke morbility and mortality despite low cardiovascular disease rate in the country. This prevalence is similar to many countries, but lower than Spain (47%) and Germany (55%), and it is higher than Sweden (38%), England (42%) and Italy (38%)(3). Also in young adolescents, the prevalence is high and related with overwheight(4).

7 – Diabetes

The CHD risk in diabetics varies widely with the intensity of risk factors and causes much of the disability in patients with diabetes(55). Both the risk and the rate of development of atherosclerosis are increased in diabetics. High concentrations of glucose increase atherosclerosis-related inflammation either directly or by leading to liberation of free fatty acids which promote earlier cells apoptosis and reduce availability of nitric acid, which would otherwise enable arteries to relax and blood flow to increase.

In addition to the importance of diabetes as a risk factor, diabetics have a greater burden of other atherogenic risk factors than nondiabetics, including hypertension, obesity, increased total-to-HDL-cholesterol ratio, hypertriglyceridemia, and elevated

plasma fibrinogen. Not only type 2 diabetes (DM-2), but also impaired glucose metabolism (IGM) are associated with increased arterial stiffness from adolescence to adulthood. An important part of the increased stiffness occurs before the onset of DM-2 and is explained neither by conventional cardiovascular risk factors nor by hyperglycemia or hyperinsulinemia(56).

Diabetes seems to be the only atherosclerosis risk factor that is more pronounced in women than in men, who lose this way their sex protection(57).

8 – Dyslipidemia

The positive relationship between dyslipidemia and cardiovascular disease morbidity and mortality is one of the most consistent and established links in epidemiology. Taking into account previous studies, hypercholesterolemia in children is directly associated with coronary heart disease prevalence in adults of the same region(58). Dyslipidemia is therefore one of the most important determinants of atherosclerosis and cardiovascular disease, and our study will focus on this specific risk factor.

LIPIDS AND DYSLIPIDEMIA

Abnormalities of lipoprotein metabolism include elevations in total cholesterol, LDL-C and triglycerides, and deficiencies of HDL-C. These may be related to genetic conditions such as familial hypercholesterolemia, be secondary to other pathologies or, more frequently, may have a multifactorial origin(59-65).

Since 1970s, a great effort has been made to document the natural history of atherosclerosis, its etiopathogeny and major risk factors including dyslipidemia. Multiple studies have presented data supporting that the early stages of atherosclerosis begin in childhood. They also tried to characterize its determinants beginning in childhood, in an attempt to recognize modifiable risk factors or behaviours that could be prevented or postponed. If premature development of cardiovascular disease can be anticipated during childhood, the disease might also be prevented.

The PDAY study (Pathobiological determinants of atherosclerosis in youth) and the Bogalusa Heart Study were the first studies to document anatomic changes and to relate them with dyslipidemia. In the PDAY study, arteries and tissues from more than 2000 persons 15-34 years of age whose deaths were attributed to accidents, homicides or suicides were collected and lipids at time of autopsy were analysed. They found that the prevalence of increased coverage of the arterial intimal surface, with fatty streaks and fibrous plaques, was associated with elevation of serum cholesterol levels(66). The Bogalusa investigators followed a total and geographically well-defined community in Bogalusa, USA.

In the autopsy studies done to persons who had died for accidental causes, they also found significative association between atherosclerotic lesions and abnormalities of all lipid components(67).

Another study, the Muscatine study, that followed the health and well-being of the community of Muscatine over time, showed that children with high cholesterol are more likely to have siblings and parents with high cholesterol(68). Investigators in this study also showed that increased carotida intima media thickness measured using ultrasonography in adults aged 33-42 is associated with increased total cholesterol concentration in childhood(69). This was also noted by the European Young Finns Study, which included 3596 participants aged 3-18 years-old from all around Finland – cardiovascular risk status in adolescence, including high LDL cholesterol, was predictive of increased carotid intima media thickness and decreased elasticity in young adulthood(70).

Elevated LDL-C plays a pivotal role in atheromatous plaque development and in progression and rupture of the plaque, which causes most of the acute symptoms of acute coronary heart disease.

A low HDL cholesterol level is thought to accelerate the development of atherosclerosis because of impaired reverse cholesterol transport and possibly because of the absence of other protective effects of HDL, such as decreased oxidation of other lipoproteins.

The relationship between hypertriglyceridemia and cardiovascular diseases is less clear, but seems to be independent from other forms of dyslipidemia. Hypertriglyceridemia, especially when associated with a low HDL-C, which has antiatherogenic proprieties, is an important cardiovascular risk factor that also needs to be adequately treated(71).

Plasma serum lipids are age dependent and vary with TANNER stage. The third nacional health and nutrition examination survey 1988-94 (NHANES III), provided valuable epidemiologic data concerning dyslipidemias in USA, its distribution and trends during

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childhood and adolescence. Age-specific values of total cholesterol peak at 9-11 years of age, decrease during pubertal development and increased thereafter, in young adulthood (72). Current recommendations in USA are based on values for plasma lipid levels from the National Cholesterol Education Program(NCEP) Expert on Cholesterol Levels in Children and distributions of lipid and lipoprotein levels obtained from the Lipid Research Clinics Prevalence Study, which take into account percentile values according to age and sex(73-74). The cut off points from the NHANES appear to better predict HDL-C(75). This data has been used not only in USA but in many other countries.

The American Heart Association recognized in 2003 the importance of primary prevention of atherosclerotic cardiovascular disease in children, and stated for the first time guidelines for primary prevention beginning in childhood(21).

In July 2008 American Academy of Pediatrics replaced its 1998 cardiovascular prevention policy statement, reemphasising that children with a family history of dyslipidemia or premature cardiovascular disease should be screened for high cholesterol between 2 and 10 years of age, and additionally saying that a child should be screened with a fasting lipid profile if the family history is unknown or the child has other cardiovascular risk factors (eg., BMI at or above the 85th percentile, blood pressure at or above the 95th percentile, cigarette smoking, or diabetes)(74).

Variable tracking of lipids and lipoprotein concentration was encountered over time. Evidence is stronger for Total-C and LDL-C than for HDL-C and TG, and screening high-risk children for cholesterol levels before age 10 seems appropriated. Despite this, 25-40% of high cholesterol in children may not persist after puberty, and besides, screening using family history misses substantial numbers of children with elevated lipids(68, 76-79). Using BMI alone or combined with family history as a discriminator increases sensitivity of screening, but decreases specificity. Nevertheless, for a threshold of 85th BMI percentile, BMI alone is only 50% sensitive and has 34% of false positives(80).

Characterization of determinants of dyslipidemia in children and adolescents is still a challenge in our days. This is an important issue that could help to accomplish efficient preventive measures in childhood in order to avoid dyslipidemia associated diseases, namely cardiovascular disease.

Several questions remain unanswered, including optimal ages and intervals for screening children, cost-effectiveness of screening, or the effects of treatment of lipids in childhood on coronary heart disease outcomes.

AIM OF THIS STUDY

The EPITeen project – the cohort of 1990 – started in the academic year of 2003/2004, and participants were adolescents born in 1990, attending public and private schools in Porto. This project, involving 2943 adolescents, is the first of its kind ever-held in Portugal, and the analysis of data collected intends to provide answers to many scientific questions and essential information needed for the planning of preventive measures suitable to the Portuguese population.

The present study was carried out comprising data accessed at baseline of the Epiteen project investigation, and aims to quantify prevalence of dyslipidemia, and to identify associated characteristics in this cohort of 13-year-old adolescents.

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THE FINAL MANUSCRIPT

Dyslipidemia Among 13-year-old Adolescents:

The EPITeen Study

Abstract

Aims: To access prevalence of dyslipidemia and identify associated characteristics in an urban population of 13-year-old adolescents.

Methods: Participants were 13-year-old urban adolescents accessed at the baseline evaluation of a population-based cohort. Blood samples of 1388 adolescents were collected to obtain lipid serum values. Associations done between lipid levels and the characteristics of adolescents were evaluated by odds ratio (OR) and 95% confidence interval (95%CI) calculated using unconditional logistic regression. Self-administered questionnaires provided information of parental education and BMI, familiar history of hypercholesterolemia or diabetes, sports practice and age at menarche in girls. A physical examination was performed, including weight, height measurements and blood pressure.

Results: Abnormal high total- and LDL-cholesterol were associated with parents' history of hypercholesterolemia. Overall, dyslipidemia was present in 24.5% of the adolescents (23.4% in girls and 25.6% in boys, p=0.375) and significant association was found in relation with parent's history of hypercholesterolemia (OR=1.32 (CI95% 1,00-1,76)) and adolescents' BMI (OR=1.38 (CI95% 1,00-1,92) for overweight and 3.56 (CI95% 2.48-5.12) for obese). Boys had a higher prevalence of low HDL-cholesterolemia (14.0% vs. 9.1%, p=0.005). No significant differences in serum lipids were noted according to parents' overweight, parents' history of diabetes, adolescent sport practice or, in girls, to the age at menarche.

Conclusion: Prevalence of dyslipidemia was high. Family history of dyslipidemia and BMI were the main determinants of dyslipidemia at this age. In 13-year-old girls, lipids were not influenced by the age at menarche.

Dyslipidemia is a major contributing factor for atherosclerosis and cardiovascular diseases, the leading causes of morbidity and mortality in developed countries(1). It may be related to genetic conditions, be secondary to specific pathologies or, more frequently, it presents a multifactorial origin comprising modifiable risk factors(59-65). The processes related to the development of arteriosclerosis begin in the first decades of life, which reinforces the importance of primary prevention of atherosclerotic cardiovascular disease in children(13-16). The recognition and better characterization of determinants of dyslipidemia in children and adolescents could provide efficient measures to prevent associated diseases.

The American Heart Association (AHA) and the American Academy of Paediatrics (AAP) recognized this and delivered guidelines for primary prevention in childhood, emphasising the importance of hypercholesterolemia and early arterial cholesterol deposits on reduction in arterial elasticity. In its statement, AAP concludes recommending lipid screening of high risk children no later than 10 years of age(21, 74).

Coronary heart disease (CHD) mortality in Portugal is low and similar to that in Spain and Italy, also countries with historically low CHD rates, but Portugal presents a different pattern of cardiovascular disease, with higher stroke mortality than in most European countries(2-3). Thus, data from our study could help to understand if this difference may be explained by a different pathway from that usually found in other countries.

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On the other hand, most previous studies that have focused on determinants of dyslipidemia in children and adolescents aggregated a wide variety of ages analysed in categories of age, sometimes including a large range of age in the same cathegory(72, 81-82). As different determinants may be present or have a different impact at different ages, and as adolescence is characterized by major physical and biological changes, this aggregation may hide relevant results. Our study, while aiming to access prevalence and risk factors for dyslipidemia in 13-year-old adolescents, tries to focus on a specific age during adolescence minimizing possible residual confounding.

MATERIALS AND METHODS

Study population

Participants were 13-year-old urban adolescents, enrolled in the Epidemiological Health Investigation of Teenagers in Porto (EPITeen) cohort. Details of the study population, recruitment, and procedures have been given previously(83). Briefly, every public and private schools with 13-year-old students in Porto were approached. All public schools and 19 (79%) private schools allowed us to contact eligible students and families.
We identified 2788 eligible adolescents and a total of 2160 students (1651 from public and 509 from private schools) agreed to participate and provided information for at least part of the planned assessment. This resulted in a 77.5% overall participation rate, similar in public and private schools (77.7% vs. 77.0%, p = 0.709).

The evaluation included two self-administered questionnaires (one completed at home, the other at school) and a physical examination, performed at school, between 8 a.m. and 10 a.m., by a team of experienced nurses, nutritionists and physicians. A 12-h overnight fasting blood sample was obtained from 1388 (64.2%) consenting participants.

The Ethical Committee of the University Hospital of São João, Porto, approved the study. Parents and adolescents received written information, detailing the purpose and the design of the study. Additionally, the study was described and discussed in all schools, or special meetings arranged according to parents' convenience. Written informed consent was obtained from both parents and adolescents, with a specific consent for the blood collection.

Questionnaires

One first questionnaire inquired about demographic, social, behavioural and clinical characteristics of the adolescent and the family, and was self completed at home. Further information concerning physical activity and behaviours was answered by the adolescent at school during the research team visit through a second written questionnaire.

The parent's years of complete schooling were used as an indicator of social class, and the adolescents were classified according to the parent with the highest completed grade. For each progenitor, information on previous diagnosis of diabetes, hypertension or dyslipidemia was collected. Adolescents were considered to have parents' history of diabetes, hypertension or dyslipidemia if this was referred for at least one of the parents. Parents' body mass index (BMI) was calculated based on self-reported data. BMI values between 25.0 to 29.9 kg/m^2 were classified as "overweight" and values ≥ 30 kg/m^2 were classified as "obese"(84). The highest BMI class of the parents was chosen to represent parents' BMI. Practice of sports was considered as any exercise planned, regular and carried out as extra-curricular activities, independently of frequency or intensity.

Physical examination

Anthropometric measurements were obtained with the subjects in light indoor clothes and no shoes. Body mass index (BMI) was classified as "normal weight" if <85th percentile, "overweight" if ≥85th percentile and <95th percentile, or "obese" if ≥95th percentile,

according to the age- and sex-specific body mass index reference percentiles developed by the United States Centres for Disease Control and Prevention(85).

Blood pressure was measured using a random zero sphygmomanometer (Hawksley™, Lancing, Sussex, United Kingdom), and classified according to the recommendations of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents(86). Thus, adolescents were classified as having "hypertension" if systolic (SBP) and/or diastolic blood pressure (DBP) were above the 95th percentile for gender, age and height; and as having "pre-hypertension" if SBP and/or DBP levels were above the 90th percentile but both < the 95th percentile(86). Due to the small number of those who were above the 95th percentile, for comparisons by levels of cholesterol the last two categories were aggregated.

Blood sample and analyses

Approximately 5 ml venous blood samples were obtained from the antecubital veins and centrifuged within 1.5-2 hours. Serum total cholesterol and triglycerides were measured using conventional colorimetric methods, while HDL-Cholesterol was measured with a direct method. The within-run and the run-to-run variations for the serum concentrations of these variables were less than 10%. All this measurements were made using an Olympus AU5400™ automated clinical chemistry analyzer (Beckman-Coulter™, Izasa, Porto, Portugal). LDL-C values were estimated by the formula of Friedewald et al: $[\text{LDL-C}_{\text{Fried}}]$ = [Total cholesterol] – [HDL-C] – [TG] / 5 (87).

Dyslipidemia includes elevations in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C). Adolescents were considered to have dyslipidemia whenever TG, TC or LDL-C values were above 95th percentile, or if HDL-C values were inferior to the 5th percentile for age and sex, according to "Lipid and lipoprotein distributions in subjects

aged 5 to 19 years", adapted from the Lipid Research Clinic Pediatric Prevalence Study(74). No adolescent had TG levels above 400mg/dl.

Statistics

Serum values of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were compared using the student's t-test or Anova, and for triglycerides the nonparametric equivalent tests were used.

Associations between dyslipidemia or each one of its components and the characteristics of adolescents were evaluated by odds ratios (OR) and 95% confidence intervals (95%CI) calculated using unconditional logistic regression. Models were fitted with adjustment for variables that presented a statistically significant effect in univariate analyses and were considered to sustain a plausible biological and temporal relationship with the outcome. The significance level was set at 5% and analyses were performed using SPSS 16.0™.

RESULTS

The analyses were done in 1388 adolescents (725 girls and 663 boys) who agreed to take a fast blood sample. No statistical significant differences were found between adolescents with and without blood sample regarding type of school, sex, parental education, parents' history of hypercholesterolemia, BMI, regular practice of sports or age at menarche in girls (table 1). Adolescents who didn't collect a blood sample were mainly the ones who had not performed the physical examination, contributing to a large proportion of missing data at this stage.

Girls presented higher lipid levels than boys, even though these differences were only significant for TG (median 0.61 g/L vs. 0.55 g/L, p<0.001). Nevertheless, when we considered cut-offs to compare prevalence of abnormal values, statistically significant differences were found only for abnormal HDL-C prevalence, higher in boys (14.0% vs.

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9.1%, p=0.005). Overall dyslipidemia, presented as high values for TC or LDL-C, low HDL-C and/or hypertriglyceridemia was present in 24.5% of the adolescents (23.4% in girls and 25.6% in boys, p=0.375) (table 2).

In general, no significant differences on continuous values of serum lipids were noted according to parents' overweight, parents' history of diabetes, adolescent sport practice or, in girls, to the age at menarche (table 3). High TC and LDL-C levels were present in girls and boys with parents' history of hypercholesterolemia. According to BMI, HDL-C values dropped from 0.51 ±0.11 g/L if BMI <85th percentile to 0.42±0.09 g/L if BMI >= 95th percentile (p<0.001) in girls, and in boys from 0.50±0.12 g/L to 0.40± 0.10 g/L (p<0.001), respectively. HDL-C values also decreased in boys with parents' obesity or high blood pressure and in girls with parents' history of diabetes. TG increased significantly with adolescent BMI classes. In addition, a positive relation was found between TG levels and adolescent high blood pressure, and TG levels and parents' history of hypercholesterolemia, both being significant in girls (table 3).

Considering cut-offs for lipids and after adjustments, overweight and obese adolescents maintained a higher probability of having abnormal serum values in all evaluated parameters. Males presented a significantly higher probability of having a low HDL-C. Additionally, we found parent's history of hypercholesterolemia significantly associated with abnormal levels of TC, and LDL-C. The association between parent's history of hypercholesterolemia and abnormal TG levels was marginally significant. In regard to parental education, hypertriglyceridemia was less frequent in those classified in the lower class, who was representing families with poorer income/lower socioeconomic status. Nevertheless, the relationship among the other categories did not differ and we could not find a trend, as all presented odds near 2 when compared with the lower class. For overall dyslipidemia, we found a significant association with parent's history of hypercholesterolemia and adolescents' BMI (table 4).

DISCUSSION

As reported on other population based studies comprising children and adolescents, the prevalence of dyslipidemia and hypercholesterolemia is high(72, 88-90), in our study almost a quarter of the adolescents having dyslipidemia at this age. The most frequent form of dyslipidemia was a low HDL-C, and the least frequent the hypertriglyceridemia.

Mean cholesterol values are similar to those of the Bogalusa Heart Study, Lipid Research Clinic Pediatric Study and NHANES III data(82, 88, 91). Despite this, they are inferior to the ones reported on school-aged Muscatine Study children and also to European studies like the Young Finns Study, or the Four Provinces Study in Spain(50, 92-93). The higher values pointed on both the Muscatine and Spanish studies could be explained by the younger age of their participants, as it is known that cholesterol levels peak at ages 9-11, and then drop during puberty(50, 72, 88).

Puberty is an important determinant of cholesterol levels(68, 94-95). In our study, despite homogeneity in our age sample of 13-yeard-old adolescents, some variability in puberty development may be expected. However, recruitment and examination at school limited conditions to access Tanner stage of puberty in both genders. Thus, as there is not an easy recalled puberty marker in boys, puberty was only evaluated in girls according to the age at menarche. Our inability to observe significant differences in cholesterol levels according to categories of age at menarche, either as continuous values or considering data as above or under desirable levels, could be related to misclassification resulting from the use of age at menarche as puberty marker. On the other hand it is also possible that homogeneity in the age sample could attenuate differences on puberty stage and make it impossible to be detected. Moreover, the age sample may be a strong point in our study regarding that up to forty per cent of pre-pubertal cholesterol levels do not persist after sexual maturation(68, 77, 79), and at this age lipid levels may be a more specific predictor of future coronary disease. This could support lipids screening at this age as a

better indicator to identify those apparently non-high risk children with dyslipidemia, rather than that performed at younger ages.

HDL-C is lower in males than in females throughout life(96-97). We found a higher prevalence of low HDL-C in boys, which could contribute to higher prevalence of coronary heart disease on adult men. This may be related to sex-specific effects on cardiovascular risk factors presented at this age, supporting that gender effect starts early in adolescence.

In general, we found significant differences according to family history of hypercholesterolemia considering mean lipid values as continuous variables and regarding the classification as discrete variables. This highlights the strength of association of genetic or other family shared factors contributing to hypercholesterolemia even at this young age, and reinforces the family history of hypercholesterolemia as an important marker to recognize targets for screening and preventive measures beginning on childhood(74, 98). It is important to note that our association may have been underestimated given that family history was defined based solely on self-reported parents' data. Some adolescents probably were considered not to have family history of hypercholesterolemia just because their parents were relatively young – 32% of the mothers and 17% of the fathers were aged under 40 – and may not have known of this asymptomatic health risk factor. Thus, we need to be aware that parents' history is an important but not a sensitive sign of dyslipidemia at this young age.

Obesity constitutes one of the major problems and challenges for Public Health systems in Western countries, and childhood obesity has been systematically associated with unfavourable lipid profile(50-51), in particular to higher plasma TG and lower HDL-C levels. These are typical metabolic findings of obesity in adults, which were corroborated in our 13-year-old adolescents' study, and it reinforces the need of a more vigorous approach to prevention and treatment of obesity early in life. This is of critical importance given that obesity has been also associated to other risk factors for atherosclerosis like hypertension, insulin resistance and glucose intolerance(52).

Hypertension is another biological factor that usually clusters with unfavorable lipid profile. We found hypertension mainly linked to obesity and therefore we did not consider it as an individually important determinant to take into account, even though it confirms previous data that describes the cluster of cardiovascular risk factors at young ages(53).

Previous works on adolescents have demonstrated that physical activity may be related to a healthier lipid profile(43). Nevertheless, physical fitness seems to have a greater effect on serum lipids when compared to the level of physical activity(42, 99). In our study while considering lipids as continuous variables, we could not find any significant differences concerning practice of sports, but we found a trend showing a possible independent protective effect of sport practice on abnormal TC, LDL-C and TG, or when dyslipidemia was considered as a whole. The lack of overt association between practice of sports and dyslipidemia in our study could be explained by the lower discriminatory power of the measure of practice of sports rather than aerobic capacity or muscle strength as cardiovascular health indicators. Eventually, lack of association could also reflect the low number of participants engaging in sports or otherwise that those practicing sports were not getting enough activity to achieve a healthy lipid-metabolic profile.

One of the strengths of our study is that population is representative of 13-year-old adolescents, considering the overall participation rate of 77.5% and the fact that attendance to school is still compulsory at this age. Furthermore, no significant differences were found between those who agreed and not agreed to take a blood sample. There were also no blood samples with values of TG above 400 mg/dl, and therefore accuracy of Friedwald formula is not an issue in this group of adolescents.

CONCLUSION

Dyslipidemia in adolescents was considerably common in both genders. Family history of dyslipidemia and BMI were the main determinants at this age, which reinforces these groups as target for early detection and control of dyslipidemia in order to effectively prevent atherosclerosis. Lipids at 13-year-old were not influenced by age at menarche, although further study is necessary to confirm this and to determine whether this age is more adequate than a younger prepubertal/beginning of puberty age to screen non-high risk children for dyslipidemia and future cardiovascular disease.

TABLES

Table 1 – Comparison of demographic, behavioural and anthropometric characteristics between adolescents with or without a blood sample

	Blood Sample		
	no 773	Yes 1388	p value
Type of school			
Private	167 (21.6)	373 (24.7)	0.115
Sex			
Female	390 (50.5)	725 (52.2)	0.454
Parents Education (years)			
$\leq$4	112 (16.6)	191 (15.0)	
5-9	195 (28.9)	427 (33.5)	
10-12	176 (26.1)	348 (27.3)	0.072
>12	191 (28.3)	307 (24.1)	
Missing	99	115	
Hypercholesterolemia in parents			
None	340 (60.0)	651 (58.3)	0.555
At least one	227 (40.0)	465 (41.7)	
Missing or unknown	206	272	
Adolescent BMI			
<85 percentile	493 (75.4)	1002 (72.3)	
$\geq$85-95 percentile	98 (15.0)	238 (17.2)	0.329
$\geq$95 percentile	63 (9.6)	146 (10.5)	
Missing	119	2	
Regular practice of sports			
No	292 (49.9)	629 (50.0)	
Yes	293 (50.1)	630 (50.0)	0.985
Missing	188	129	
Girls' age of menarche			
>=13 years-old	108 (35.5)	227 (32.4)	
12 years-old	105 (34.5)	248 (35.4)	
11 years-old	63 (20.7)	160 (22.8)	0.776
8-10 years-old	28 (9.2)	66 (9.4)	
Missing	86	24	

Table 2 – Description cholesterol, triglycerides values, and prevalence of abnormal values of lipids, by sex

Lipids	Girls (n=725)	Boys (n=663)	p value
Total cholesterol* >P95	1.69 +/- 0.31 n=70 (9.7%)	1.61 +/- 0.30 n=62 (9.4%)	p=0.751 p=0.919
LDL-Cholesterol* >P95	1.06 +/- 0.25 n=74 (10.2%)	1.01 +/- 0.25 n=61 (9.2%)	p=0.117 p=0.588
HDL-Cholesterol* <P5	0.49 +/- 0.11 n=66 (9.1%)	0.48 +/- 0.12 n=93 (14.0%)	p=0.401 p=0.005
Triglycerides (median P25, P75) >P95	0.61 (0,49; 0,81) n=35 (4.8%)	0.55 (0,42; 0,74) n=32 (4.8%)	p<0.001 p=1
Dyslipidemia **	n=170 (23.4%)	n=170 (25.6%)	p=0.375

* presented as mean+/- standard deviation; **at least one abnormal value of lipids

Table 3 (next page) - Levels of serum lipids by sociodemographic characteristics, parents' history of disease, and adolescent BMI, blood

	Total-Cholesterol (g/l)		LDL-Cholesterol (g/l)		HDL-Cholesterol (g/l)		Triglycerides (g/l)	
	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys
Parents BMI								
Normal	1,71 +/- 0,32	1,64 +/- 0,30	1,07+/-0,27	1,03 +/- 0,25	0,50 +/- 0,11	0,48 +/- 0,11	0,62 (0.49-0.82)	0.55 (0.42-0.72)
Overweight	1,68 +/- 0,30	1,61 +/- 0,32	1,05+/-0,24	1,00 +/- 0,26	0,50 +/- 0,11	0,49 +/- 0,12	0,59 (0.49-0.77)	0.56 (0.42-0.73)
Obesity	1,67 +/- 0,30	1,56 +/- 0,28	1,06+/-0,23	0,99 +/- 0,23	0,48 +/- 0,12	0,45 +/- 0,11	0,61 (0.50-0.85)	0.53 (0.42-0.76)
	p=0,449	**p=0,151**	**p=0,723**	**p=0,302**	**p=0,146**	**p=0,027**	**p=0,415**	**p=0,988**
Parents with dislipidemia								
No	1,65 +/- 0,28	1,58 +/- 0,29	1,02 +/- 0,23	0,98 +/- 0,24	0,49 +/- 0,11	0,48 +/- 0,11	0,59 (0.49-0.77)	0.55 (0.42-0.73)
yes	1,77 +/- 0,33	1,66 +/- 0,34	1,13 +/- 0,26	1,05 +/- 0,27	0,50 +/- 0,11	0,48 +/- 0,11	0,67 (0.52-0.86)	0.57 (0.42-0.75)
	p<0,001	**p=0,003**	**p<0.001**	**p=0,001**	**p=0,693**	**p=0,807**	**p=0,008**	**p=0,670**
Parents with diabetes								
No	1,70 +/- 0,31	1,61 +/- 0,30	1,06 +/- 0,25	1,01 +/- 0,26	0,50 +/- 0,11	0,48 +/- 0,11	0.61 (0.49 – 0.81)	0.55 (0.42-0.74)
yes	1,65 +/- 0,28	1,54 +/- 0,25	1,06 +/- 0,23	0,96 +/- 0,21	0,46 +/- 0,11	0,47 +/- 0,10	0.57 (0.50-0.73)	0.55 (0.41-0.76)
	p=0,242	**p=0,147**	**p=0,864**	**p=0,177**	**p=0,022**	**p=0,424**	**p=0,305**	**p=0,882**
Adolescent BMI								
Normal	1,70 +/- 0,30	1,61 +/- 0,30	1,06 +/- 0,25	1,00 +/- 0,25	0,51 +/- 0,11	0,50 +/- 0,12	0,60 (0.49-0.77)	0.53(0.41-0.77)
Overweight	1,68 +/- 0,32	1,58 +/- 0,27	1,06 +/- 0,24	1,01 +/- 0,22	0,47 +/- 0,11	0,44 +/- 0,08	0,65 (0.49-0.91)	0.53 (0.43-0.76)
Obesity	1,66 +/- 0,31	1,62 +/- 0,34	1,08 +/- 0,25	1,06 +/- 0,28	0,42 +/- 0,09	0,40 +/- 0,10	0,72 (0.54-1.02)	0.80 (0.42-1.07)
	p=0,691	**p=0,542**	**p=0,729**	**p=0,172**	**P<0,001**	**p<0,001**	**p=0,002**	**p<0,001**
Adolescent Blood Pressure								
Normal	1,68+/-0,28	1,62 +/- 0,31	1,06 +/- 0,22	1,01 +/- 0,25	0,50 +/-0,11	0,49 +/- 0,12	0.60 (0.48-0.77)	0.54 (0.41-0.70)
BP >P90	1,71 +/-0,34	1,58 +/- 0,30	1,07 +/-0,28	1,00 +/-0,25	0,49 +/-0,11	0,46 +/- 0,11	0.65 (0.51-0.87)	0.57 (0,44-0.80)
	p=0,407	**p=0,105**	**p=0,648**	**p=0,634**	**p=0,800**	**p<0,001**	**p=0,006**	**p=0,060**
Sports practice								
No	1,70 +/- 0,32	1,60+/-0,31	1,06+/-0,26	1,00+/-0,25	0,49+/-0,11	0,47+/-0,11	0.62(0.51-0.81)	0.57(0.45-0.75)
yes	1,69+/-0,28	1,62+/-0,31	1,06+/-0,22	1,01+/-0,25	0,50+/-0,10	0,48+/-0,12	0.60(0.48-0.80)	0.53 (0.41-0.73)
	p=0,748	**p=0,473**	**p=0,741**	**p=0,617**	**p=0,513**	**p=0,178**	**p=0,201**	**p=0,122**
Age of menarcAge								
>=13 years-old	1,70 +/-0,29		1,05 +/-0,22		0,51 +/-0,12		0,63 (0,51-0,81)	
12 years-old	1,71+/-0,32		1,08+/-0,28		0,49+/-0,10		0.60 (0.49-0.80)	
11 years-old	1,67+/-0,31	----------	1,05+/-0,24	-----------	0,48+/-0,12	------------	0,61 (0.49-0.78)	--------------------
8-10 years-old	1,67+/-0,26		1,05+/-0,22		0,48+/-0,10		0.58 (0.47-0.82)	
	p=0,586		**p=0,519**		**p=0,101**		**p=0,821**	

	Total-Cholesterol		LDL-Cholesterol		HDL-Cholesterol		Tryglicerids		Dyslipidemia	
	O.R.r	O.R.adjust.*	O.R.r	O.R.adjust. **	O.R.r	O.R.adjust.***	O.R.r	O.R.ajust.***	O.R. r	O.R. adjust.****
Private school	0,89 (0,58-1,36)	0,79 (0,51-1,24)	0,74 (0,48-1,15)	0,74 (0,47-1,15)	0,78 (0,52-1,16)	0,77 (0,51-1,16)	0,52 (0,26-1,03)	0,51 (0,26-1,02)	0,70 (0,52-0,95)	0,69 (0,50-0,95)
Sexo 1 (male)	0,96 (0,67-1,38)	0,96 (0,67-1,38)	0,89 (0,62-1,27)	0,89 (0,62-1,27)	1,63 (1,17-2,28)	1,64 (1,16-2,30)	1,00 (0,61-1,63)	0,98 (0,59-1,61)	1,13 (0,88-1,44)	1,19 (0,92-1,54)
Parents Education (years)										
<4	1	1	1	1	1	1	1	1	1	1
5-9	1,93 (0,97-3,81)	2,02 (1,01-4,01)	1,22 (0,67-2,23)	1,28 (0,70-2,36)	1,99 (1,10-3,60)	2,02 (1,10-3,70)	0,71 (0,35-1,45)	0,68 (0,33-1,41)	1,48 (0,98-2,22)	1,54 (1,01-2,34)
10-12	1,89 (0,94-3,80)	1,97 (0,97-4,00)	1,30 (0,70-2,41)	1,35 (0,72-2,53)	1,23 (0,65-2,32)	1,26 (0,66-2,42)	0,75 (0,36-1,56)	0,75 (0,35-1,58)	1,14 (0,75-1,76)	1,26 (0,81-1,97)
>12	1,97 (0,97-4,00)	2,14 (1,04-4,39)	1,23 (0,65-2,31)	1,34 (0,70-2,56)	1,32 (0,69-2,51)	1,44 (0,75-2,79)	0,51 (0,22-1,55)	0,54 (0,23-1,25)	1,12 (0,72-1,73)	1,33 (0,84-2,11)
Parents BMI										
Normal	1	1	1	1	1	1	1	1	1	1
Overweight	0,87 (0,58-1,31)	1,94 (0,54-1,25)	0,78 (0,52-1,19)	0,72 (0,47-1,10)	0,99 (0,65-1,51)	0,91 (0,59-1,41)	0,80 (0,43-1,47)	0,72 (0,39-1,33)	0,92 (0,68-1,24)	0,86 (0,63-1,17)
Obesity	0,62 (0,35-1,10)	0,53 (0,29-0,96)	0,83 (0,49-1,39)	0,63 (0,37-1,10)	1,68 (1,05-2,70)	1,21 (0,74-1,99)	1,31 (0,67-2,59)	0,86 (0,42-1,75)	1,28 (0,90-1,83)	0,97 (0,66-1,43)
Parents hypercholesterolemia	1,58 (1,06-2,35)	1,63 (1,09-2,43)	1,93 (1,30-2,88)	2,04 (1,36-3,06)	0,78 (0,53-1,16)	0,77 (0,51-1,15)	1,66 (0,97-2,84)	1,67 (0,97-2,89)	1,28 (0,97-1,69)	1,32 (1,00-1,76)
Parents history of Diabetes	0,16 (0,04-0,67)	0,16 (0,04-0,67)	0,80 (0,39-1,64)	0,68 (0,33-1,41)	1,16 (0,64-2,10)	1,13 (0,61-2,08)	0,57 (0,18-1,88)	0,54 (0,16-1,79)	0,89 (0,56-1,42)	(1) 0,78 (0,48-1,29) (2) 0,63 (0,37-1,06)
Adolescent BMI										
Normal	1	1	1	1	1		1		1	1
Overweight	0,92 (0,55.1,52)	0,89 (0,53-1,48)	1,03 (0,63-1,68)	1,00 (0,61-1,64)	1,87 (1,22-2,87)		2,33 (1,25-4,36)		1,42 (1,03-1,97)	1,38 (1,00-1,92)
Obesity	1,68 (1,01-2,80)	1,70 (1,01-2,84)	1,89 (1,15-3,11)	1,91 (1,16-3,14)	4,68 (3,07-7,14)		5,44 (3,02-9,80)		3,56 (2,48-5,10)	3,56 (2,48-5,12)
Adolescent Blood Pressure >P90	1,13 (0,78-1,64)	1,09 (0,74-1,60)	1,21 (0,84-1,74)	1,12 (0,77-1,64)	1,57 (1,12-2,20)	1,22 (0,86-1,74)	1,28 (0,78-2,10)	0,91 (0,54-1,54)	1,46 (1,14-1,88)	1,24 (0,95-1,62)
Sport practice	0,86 (0,59-1,26)	0,80 (0,54-1,19)	0,73 (0,50-1,07)	0,73 (0,50-1,06)	0,95 (0,67-1,35)	1,00 (0,70-1,43)	0,61 (0,36-1,06)	0,64 (0,37-1,12)	0,76 (0,59-0,99)	0,79 (0,60-1,04)
Menarche										
>=13 years-old	1	1	1	1	1	1	1	1	1	1
12 years-old	1.12 (0,24-5.18)	1,25 (0,27-5,89)	1,06 (0,23-4,85)	1,19 (0,26-5,52)	0,51 (0,06-3,96)	0,55 (0,07-4,37)	2,20 (0,45-10,84)	2,46 (0,49-12,32)	1,13 (0,58-2,18)	0,87 (0,44-1,75)
11 years-old	1.01 (0,36-2,86)	0,98 (0,34-2,84)	0,95 (0,34-2,67)	0,89 (0,31-2,55)	1,16 (0,44-3,06)	0,82 (0,30-2,22)	1,15 (0,30-4,39)	0,79 (0,20-3,12)	1,41 (0,88-2,26)	1,24 (0,76-2,04)
8-10 years-old	1.66 (0,84-3,31)	1,63 (0,81-3,28)	1,66 (0,85-3,25)	1,61 (0,81-3,20)	1,47 (0,74-2,93)	1,22 (0,60-2,47)	1,44 (0,56-3,72)	1,17 (0,45-3,08)	1,22 (0,79-1,89)	1,13 (0,72-1,77)

o Table 4 Risk estimates of dyslipidemia and their components according to adolescents' characteristics* OR adjusted to adolescent BMI, parents dyslipidemia and parents education; **OR adjusted to adolescent BMI and parents' dyslipidemia; ***OR adjusted to adolescent BMI; **** OR adjusted to adolescent BMI, parents dyslipidemia, parents education and sports practice

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