Plasminogen activator inhibitor-1(PAI-1), PAI-1 gene polymorphism, and family history of cardiovascular disease in relation to metabolic parameters in a sample of obese children

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Abbreviations
BMI: Body Mass Index, CVD: Cardiovascular Disease: FH: Family History, PAI-1: Plasminogen Activator Inhibitor- 1

Background

PAI-1 is a serine protease inhibitor, secreted largely by endothelial and adipose cells, that functions as the principal inhibitor of tissue plasminogen activator (tPA) and urokinase (uPA), the activators of plasminogen and hence fibrinolysis. PAI-1 is present in increased levels in various disease states (such as cancer), as well as in obesity, insulin resistance, dyslipidaemia and cardiovascular disease (CVD)*. It has been linked to the increased occurrence of atherothrombosis in patients with these conditions. Studies have shown a relationship between plasma PAI-1 levels and the 4G/5G gene polymorphism in the PAI-1 gene. Children with a family history (FH)** of CVD have twice the risk of developing cardiovascular disease.

Cardiovascular disease (CVD) includes all the diseases of the heart and circulation including coronary heart disease (angina and heart attack), heart failure, congenital heart disease and stroke.

**FH of CVD (Definition): A FH of early-age CVD is defined as a parent or grandparent who had a heart attack, a stroke, or peripheral vascular disease before the age of 56 years for men or 66 years for women*

Objective and hypotheses

To assess the relationship between PAI-1 plasma concentration, PAI-1 4G allele gene polymorphism, FH of CVD and metabolic parameters in a sample of obese/overweight Greek children and adolescents.

Methods

195 subjects,106 obese/overweight (median age 10.7 years, range 2.25-17.41) and 89 age-matched healthy controls (median age 10 years, range 3.72-17.51) were studied. Anthropometric measurements taken from all subjects included weight and height, thus Body Mass Index (BMI) was calculated for each subject as Wt/Ht^2 (kg/m²). FH of CVD was obtained from all participants. Serum levels of glucose, insulin, PAI-1 levels were measured and the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. The PAI-1 4G/5G gene polymorphism was studied with polymerase chain reaction-restriction fragment length polymorphism (figure 1). Descriptive statistics and the t-test were used for data analysis.

Figure 1. Demographic data
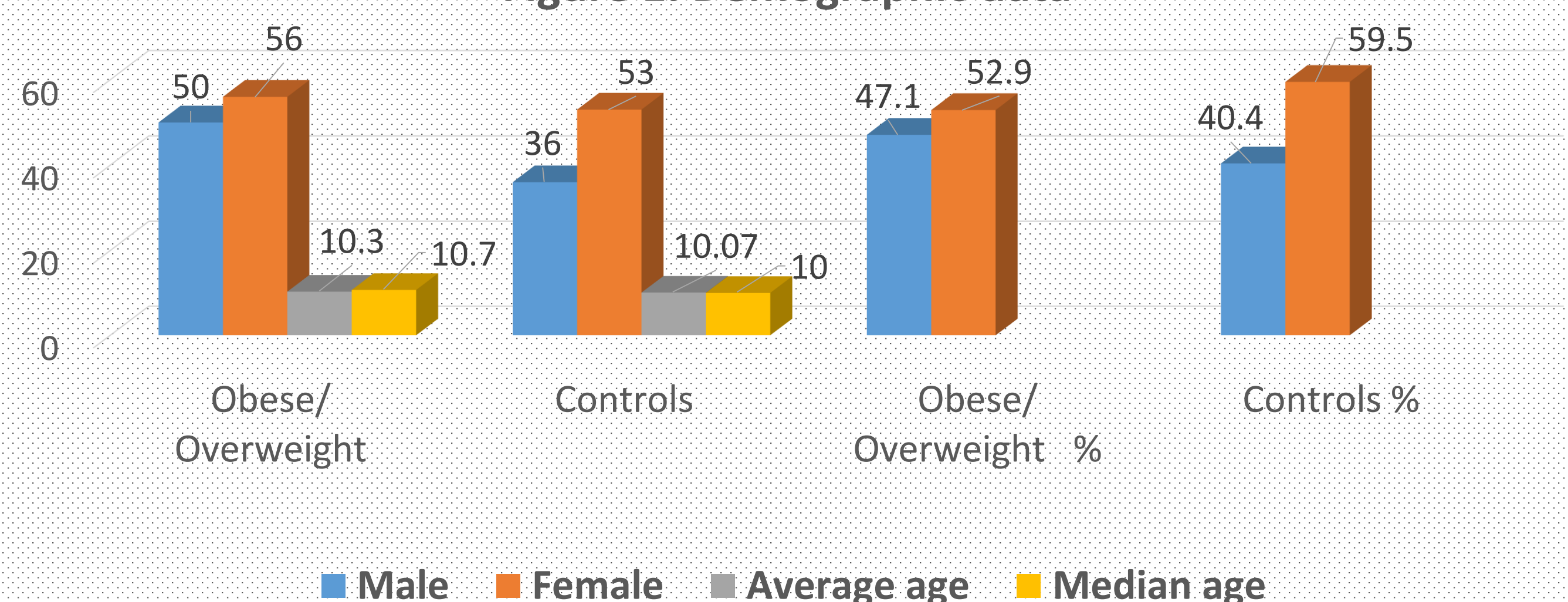
Results

The prevalence of insulin resistance (HOMA-IR) in the obese/overweight group was significantly higher (17.9%) than in the normal-weight group (7.8%), (p<0.05). Frequencies of the PAI-1 gene polymorphisms were 36.8% (4G/4G), 28.3%(4G/5G), 18.8%(5G/5G) in the obese/overweight group and 22.5%(4G/4G), 21.7%(4G/5G), 31.4%(5G/5G) in the control group. FH of CVD was positive in 67.9% of the obese/overweight group compared to 66.2% of controls, and statistically significant (p < 0.05) for the PAI-1 gene 4G/4G and 4G/5G polymorphisms, 36.8%, 28.3% and 22.5%, 21.7% respectively. HOMA-IR and PAI-1 median plasma levels also significantly correlated in the obese/overweight group compared to controls, p < 0.05 (fig.2,table 1).
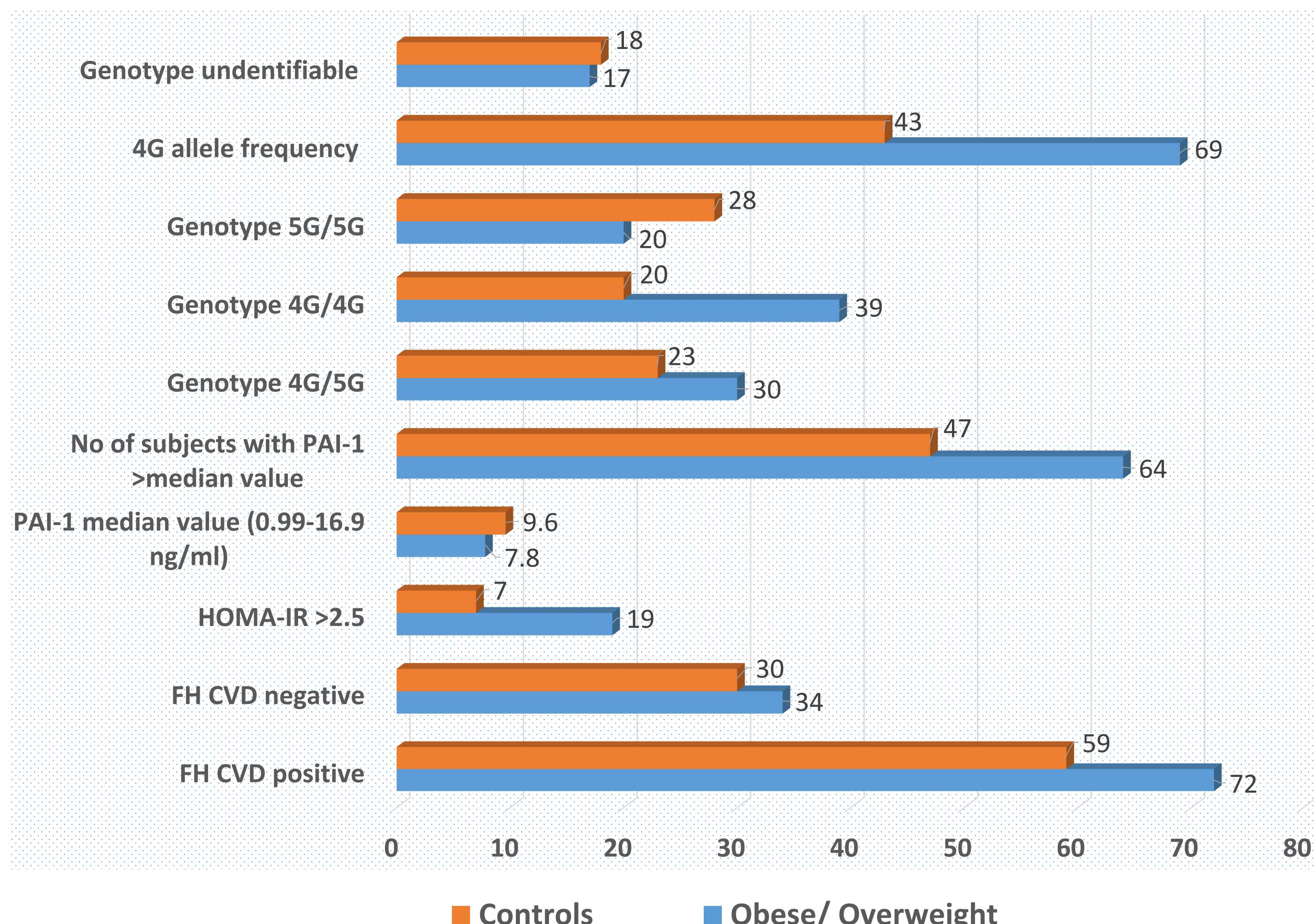

Figure 2. Results

Table 1. Results

Number	Obese/ Overweight	Controls	p value
FH CVD positive	72 (67.9 %)	59 (66.2 %)	<0.05
FH CVD negative	34 (32 %)	30 (33.7 %)	
HOMA-IR >2.5	19 (17.9 %)	7 (7.8 %)	<0.05
PAI-1 median (0.99-16.9 ng/ml)	7.8 (range 1.4-24.1)	9.6 (range 3.8-22)	
PAI-1 > median	64 (60.3 %)	47 (52.8 %)	<0.05
Genotype 4G/4G	39 (36.8 %)	20 (22.5 %)	<0.05
Genotype 4G/5G	30 (28.3 %)	23 (21.7 %)	<0.05
Genotype 5G/5G	20 (18.8 %)	28 (31.4 %)	
4G allele frequency	69 (65.1%)	43 (48.3%)	<0.004
Genotype unidentifiable	17 (16 %)	18 (20.2 %)	

Conclusion

Our study showed that the obese / overweight children had a higher frequency of a positive FH of CVD and the 4G/4G, 4G/5G genotypes of the PAI-1 gene compared to controls. Elevated PAI-1 levels appear to increase the risk of atherothrombotic events and may also promote the progression of vascular disease (Vaughan, 2005). PAI-1 levels predict the development of diabetes independently of insulin resistance suggesting that PAI-1 is a pathophysiological pathway distinct from hyperinsulinemia *(Gilardini et al, 2011)*. A recent meta-analysis has revealed that the PAI-1 4G allele (4G/4G and 4G/5G genotype) was associated with an increased risk of myocardial infarction compared with the 5G allele *(Zoller 1998, Li-Li Gong et al., 2012)*. The 4G/4G genotype has been shown to be associated with thrombotic disorders *(Balta et al, 2002)*. Therefore, the above patients are potentially at increased risk for developing vascular disease. High HOMA-IR value can also reflect the high risk of vascular disease *(Kinik et al, 2002, Berberoglu et al, 2006)*. Metabolic abnormalities are also significantly higher in children who have FH of CVD *(Sangun O et al, 2011)*.

In conclusion, the 4G allele of the PAI-1 gene promoter may be an increased risk factor for the development of thrombosis *(Nikopoulos et al, 2014)*. In addition, multiple factors, including genetic, environmental, cultural and socio-economic status may influence children's weight and may commonly persist in later life. They are particularly strong predictors of subclinical atherosclerosis in young adults. However, further studies are needed to draw a definite conclusion.

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