IIRO FAGER

SOCIOECONOMIC STATUS IN EARLY ADULTHOOD AND THICKNESS OF THE ARTERIAL WALL

University of Turku
Faculty of Medicine
Research Centre of Applied and Preventive Cardiovascular Medicine
Advanced medical studies
Supervised by Prof. Katja Pahkala and MD, PhD Elina Puolakka

TURUN YLIOPISTO

Lääketieteellinen tiedekunta
Sydäntutkimuskeskus
IIRO FAGER: Nuorten aikuisten sosioekonominen asema ja valtimon seinämän paksuus
Syventävien opintojen kirjallinen työ, 32 s
Tammikuu 2025

TIIVISTELMÄ

Sepelvaltimotauti on maailman yleisin kuolinsyy. Sosioekonomisen aseman on osoitettu olevan yksi merkittävistä sepelvaltimosairastavuuteen yhteydessä olevista tekijöistä. Tämän tutkimuksen tavoitteena oli tutkia sosioekonomisen aseman yhteyttä valtimon sisäseinämän paksuuteen (intima-media thickness [IMT]) nuorilla aikuisilla. IMT:n paksuuntuminen on yksi varhaisimmista ateroskleroosin kehittymiseen liittyvistä muutoksista.

Syventävien opintojen kirjallinen työ koostuu aiheeseen liittyvästä kirjallisuusosasta sekä empiirisestä tutkimusosasta. Tutkimusosassa aineistona käytettiin Sepelvaltimotaudin Riskitekijöiden Interventioprojektia (STRIP). Vuonna 1989 alkunsa saaneessa STRIP-tutkimuksessa aloitti 1116 tervettä vuosien 1989-1991 välillä syntynyttä lasta, joita on toistuvasti seurattu 26 vuoden ikään saakka (n=551). Kaulavaltimon sekä vatsa-aortan IMT-kaikukuvaus tehtiin 11, 13, 15, 17, 19 ja 26 vuoden iässä. Tässä tutkimuksessa sosioekonomisen aseman mittarina toimivia ammattia ja koulutusastetta selvitettiin kyselylomakkeella 26 vuoden iässä.

Tutkimuksessa ei havaittu tilastollisesti merkitsevää yhteyttä nuorten aikuisten sosioekonomisen aseman ja valtimon sisäseinämän paksuuden välillä. Löydösten puute ei sulje pois nuorten aikuisten sosioekonomisen aseman yhteyttä valtimoterveyteen, vaan vastaavat tutkimukset tämän tutkimuksen tuloksen vahvistamiseksi – tai kumoamiseksi – ovat tarpeen.

ASIASANAT: Nuoret aikuiset, sosioekonominen asema, kardiovaskulaarinen terveys, valtimon seinämän paksuus

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ABBREVATIONS

Apo B	Apolipoprotein B
BMI	Body mass index
CHD	Coronary heart disease
CVD	Cardiovascular disease
ECM	Extracellular matrix
IMT	Intima-media thickness
aIMT	Aortic intima-media thickness
cIMT	Carotid intima-media thickness
LDL	Low-density lipoprotein
SES	Socioeconomic status
STRIP	Special Turku Coronary Risk Intervention Project

1 INTRODUCTION

Ischaemic heart disease and stroke - both largely caused by atherosclerosis - are still the two most common causes of death in Finland and in the world. (1) Even though the prevalence of both has decreased significantly particularly in a working-age population, the process behind these diseases is well worth studying. It is known that the atherosclerotic process may take even decades to develop into a symptomatic disease. Furthermore, the atherosclerotic process begins in the early stages of life. The first studies to report early stages of atherosclerosis from young individuals date back to the autopsies of young male casualties of the First World War (2) Since then, very early markers of the process have been found even in babies. (3)

The inverse association of a person's socioeconomic status (SES) and cardiovascular health - along with the overall health- has been widely studied since the Whitehall I study (1967 - 1977). (3) The connection has been investigated during the whole length of the human lifespan and it is unquestionable that low SES at any stage of a person's life leads to an increased risk for cardiovascular events. The link between SES and atherosclerosis is more established in the later stages of life than it is in adolescence. Therefore, this study aims to investigate the possible association of SES at the age of 26 years with subclinical markers of atherosclerosis beginning between ages 11 and 26 years of age.

2 REVIEW OF THE LITERATURE

2.1 ATHEROSCLEROSIS

Accumulation of a plaque in the walls of arteria is called atherosclerosis – a process that can occur in any artery in the human body. The plaque builds up in the tunica intima, which is the innermost layer of an artery. Atherosclerosis is the most common underlying cause of coronary artery disease, carotid artery disease, and peripheral arterial disease. (4)

The plaque starts to form as apolipoprotein B (apoB) -containing lipoproteins are deposited in the intima. This is due to concurrent endothelial dysfunction and the exposure of vascular cells to excess lipids. More permeable and dysfunctional endothelium leads to more apoB-containing lipoproteins accumulating in the extracellular matrix of intima. Once in the extracellular matrix, apoB-containing lipoproteins particles become targets for oxidative and enzymatic modifications. Modified apoB-containing lipoproteins are pro-inflammatory and attract innate immune cells such as monocytes. Circulating monocytes migrate to the subendothelium and differentiate into macrophages. Macrophages then begin to take up modified apoB-containing lipoproteins and become filled with lipids and thus convert into foam cells. (5, 6)

This plaque build-up leads to hardening and narrowing of e.g the coronary arteria. The plaque may restrict blood flow, causing unstable angina by disturbing blood flow by obstructing the lumen of the arteria. Most of the fatal coronary events (around 76%) are caused by coronary thrombi that are formed when the plaque ruptures and exposes the thrombogenic core of the plaque. This will lead to myocardial ischemia and heart attack. (4, 7) In cerebral arteria, providing blood to the brain, atherosclerosis may cause a thrombotic stroke with the same mechanism. Of strokes 85% are ischaemic, meaning that they are caused by insufficient blood and oxygen supply to the brain. (8)

2.1.1 RISK FACTORS

The single most significant risk factor for atherosclerosis is elevated plasma or serum cholesterol concentration. Especially elevated levels of LDL cholesterol in the plasma can alone be sufficient to cause atherosclerosis without the presence of any other known risk factors. It is suggested that if all adults had less than 150mg/dl (1.7 mmol/l) of cholesterol in their plasma, symptomatic atherosclerosis would be rare. (5)

Other key risk factors include obesity, hypertension, diabetes and other inflammatory diseases, such as rheumatic diseases. They tend to accelerate a disease driven by atherogenic lipoproteins, such as LDL. However, it is not fully understood how they do it. The first theory is that they increase the atherogenicity of LDL by affecting the particle size, the number of particles or the composition of the LDL particles. The second theory is that they increase the vulnerability of the arterial wall via increasing the permeability, glycation, and inflammation. Male sex and age are also significant risk factors for atherosclerosis. (5)

Moreover, there are behavioural risk factors, such as smoking, physical inactivity, unhealthy diet, and excess alcohol consumption. Many atherogenic risk factors -such as elevated blood pressure or high blood lipid levels- are associated with these behavioural habits. (9, 10) In the Finnish working age population, the prevalence of obesity has risen, but the trends of many other risk factors have improved, such as the downward trends in the number of daily smokers and the improved quality and quantity of consumed fats. Simultaneously, there is an increasing trend in people meeting the sufficient physical activity levels. (11)

The proportion of genetic factors in the development of atherosclerosis is known to be approximately equal to that of the environmental factors. The heritability of atherosclerosis is slightly more pronounced in men compared to women. (12)

Additionally, SES is a well-known risk factor for atherosclerosis. The associations of SES and cardiovascular health, namely atherosclerosis, are addressed later in the text.

2.1.2 EARLY MARKERS

As it takes years, even decades, for overt atherosclerosis to develop, early stages of atherosclerosis can be quantified well in advance of the clinical manifestation by detecting early, subclinical markers. For instance, this can be done via non-invasive ultrasonic methods. (Figure 1 a-e) These methods are gaining popularity due to their safety and reliability. Detecting subclinical changes is useful in finding the individuals with increased risk for cardiovascular disease. Thus, early interventions can be targeted to those who most need and benefit from them. (7)

Carotid intima-media thickness (cIMT) is a subclinical marker of vascular health measured through B-mode carotid ultrasound. In practice, it is the combined thickness of the two innermost layers of an artery: tunica media and tunica intima. When a plaque starts to build

up in the arterial wall, the thickness of the wall increases. Carotid arteries originate from the aortic arch and travel up on both sides of neck, supplying blood to brains and head. Their location is easily accessible with the ultrasound, which makes them an ideal object for the imaging. By using ultrasonic cIMT assessment, even small changes in the arterial wall thickness can be detected. As an example, an increase of 0.03 mm increase per year in cIMT is associated with a 2.2-fold increase in the risk of a future coronary event. Many of the risk factors for atherosclerosis are linked to increases in the cIMT already in the childhood. Furthermore, exposure for the same risk factors in childhood is linked with cIMT increase in adulthood. (13)

IMT can be measured from the abdominal aorta as well. From autopsy studies conducted in the 1980s and 1990s, it is known that changes in the arterial wall are seen in the aorta prior to the coronary arteries. Early arterial lesions are found in the first decade of life in the aorta and in the second decade of life in the coronary arteries. (2)

Another subclinical marker and a risk factor for atherosclerosis is arterial stiffness. The elasticity of an artery depends on a regulated balance of elastin and collagen, two proteins that are important for the structure of the arterial wall. With ageing, arterial elasticity decreases as mean blood pressure and smooth muscle tone increase. These two are due to breaks in elastic fibres, accumulation of collagen, fibrosis, inflammation, medial smooth muscle necrosis and calcification. Arterial stiffness can be assessed in several ways: either non-invasively or invasively and locally or regionally. The most common and standardized method is assessment of pulse wave velocity. Pulse wave velocity is determined simply as the delay between two measuring sites along the way of the pulse wave. (14)

While cIMT and arterial stiffness are justifiably considered as markers for atherosclerosis, they may not be completely specific for the disease as they may also echo medial hypertrophy. Detection of carotid atherosclerotic plaque is a more atherosclerosis-specific indicator. Detecting the plaques (shown in figure 1) can also be done non-invasively via ultrasound. (7)

Another preclinical marker for atherosclerosis is endothelial function. The endothelium is a large endocrine organ that has multiple functions. Among others, it maintains the balance of vasoconstriction and vasodilation, synthesizes, and secretes multiple substances, and controls thrombogenesis. The endothelium becoming dysfunctional precedes the first structural atherosclerotic changes in the arterial wall. Applying ultrasonoghraphy, endothelial function

is determined by measuring the diameter of brachial artery at baseline and after increased blood flow. The precise marker is the percentual increase of luminar diameter. (15)

2.1.3 MORBIDITY

Ischaemic heart disease is the most common cause of death in Finland as well as in the world in 2018, followed by stroke. Both ischaemic heart disease and stroke are most often caused by atherosclerosis. Ischaemic heart disease is also projected to remain the leading cause of death by 2030. (1) However, their role as a cause of death has become smaller in Finland. In the 1960s, Finland had the highest coronary heart disease mortality in the world. (16). Since then, a decline of 80 % has occurred due to positive changes in the levels of risk factors in the Finnish population. A parallel change has also occurred in other developed countries. (17, 18)

In Finland, the average age of a person dying of ischaemic heart disease is concomitantly increasing; when in 1971 50 % of the men that died of ischaemic heart disease were working age (35 to 64-year-old), in 2018 the comparable number was only 10 % (19).

Figure 1 summarises atherogenesis, its key risk factors in childhood and phases of prevention (adapted from reference 7).

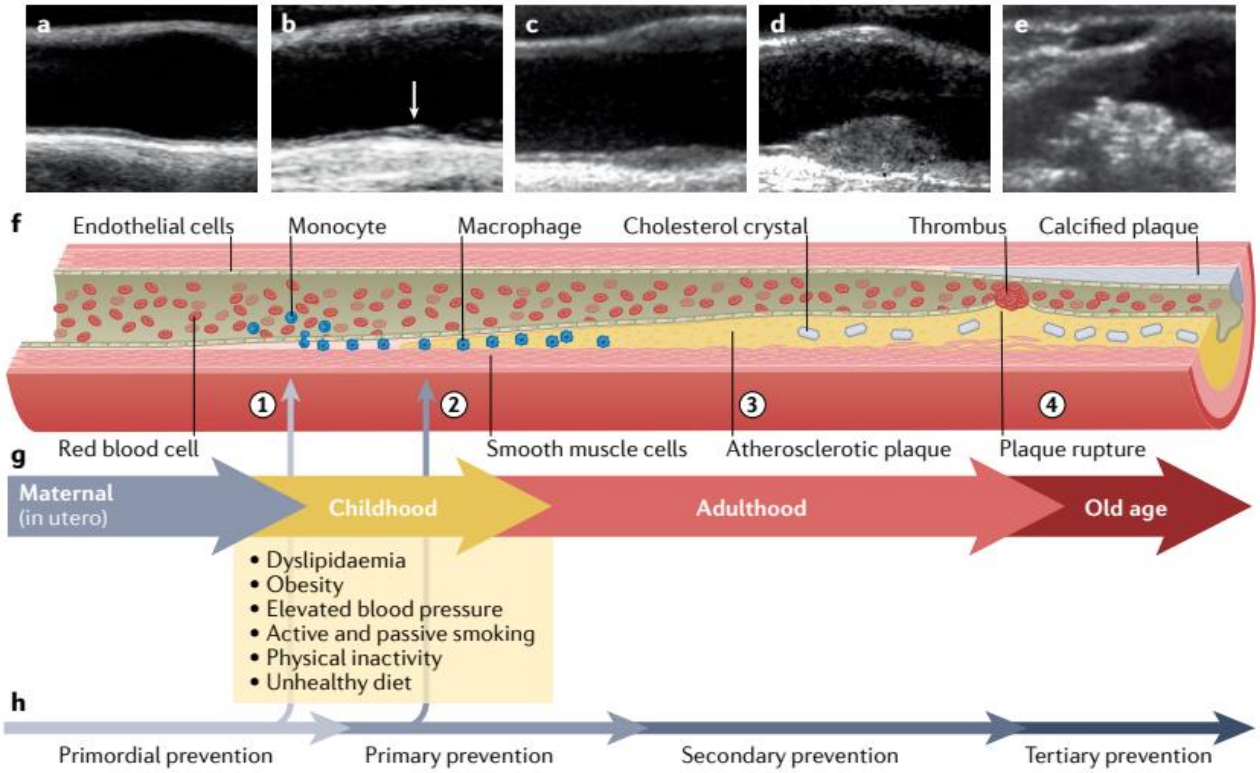


Figure 1. Progression of atherosclerosis, as visualized using carotid artery ultrasonography, risk factors during childhood and phases of prevention of atherosclerotic cardiovascular disease.

a) Normal IMT, with no atherosclerotic plaque. b) Diffuse intima–media thickening in the common carotid artery, with a small plaque in the carotid bulb (arrow). c) Diffuse intima–media thickening in the common carotid artery, with plaque formation in the far and near walls of the carotid bulb. d) Large, non-obstructing plaque in the carotid bulb protruding into the internal carotid artery. e) Large, complicated plaque obstructing the entrance of the internal carotid artery.

f) Cellular events in the arterial wall: (step 1) subtle adaptive intimal thickening, endothelial activation, and an increase in levels of proteoglycans, macrophages and lipoprotein particles in the arterial intima; (step 2) increased influx and retention of apolipoprotein B-containing lipoproteins in the intima and activation of inflammatory responses, leading to the formation of foam cells and the growth of atherosclerotic lesions; (step 3) lipoprotein-derived cholesterol forms crystals that provoke additional maladaptive responses, such as the activation of inflammatory cells and prothrombotic pathways; (step 4) clinical manifestations occur when the growing lesions disturb blood flow by obstructing the arterial lumen with thrombotic events. g) Individuals can be exposed to risk factors for atherosclerosis throughout their lifetime. [7]

2.2 SOSIOECONOMIC STATUS

SES represents a person's position in society and his/her access to social and economic resources. It consists of multiple factors that include resource-based elements such as education, occupation, income, and wealth as well as prestige-based measures linked to views of status in social hierarchy. Although these indicators strongly overlap, they measure different phenomena and thus each factor is useful. (20)

2.2.1 DIFFERENCES IN SOCIOECONOMIC STATUS IN FINLAND

Even though Finland is one of the most equal countries in the world, both economically and socially, there are some large-scale inequalities in our society. Some of the most obvious socioeconomic inequalities are related to wealth and employment. The distribution of wealth in Finland is somewhat unbalanced as the wealthiest decile of Finnish people own almost half of the net wealth available. Similar development exists in many other western countries. There is also an age-based division in the wealth of Finns: people aged 45 years or older earn significantly more money than the median while younger people earn even more significantly less money compared to the median. (21)

Finland's employment rate is considerably lower when compared to the other Nordic countries. Especially people aged over 55 years are employed poorly. While Finland has caught up on the other Nordic countries, its relatively low employment keeps creating socioeconomic inequalities. (22) While the employment rate is reasonably similar in men and women, there are several differences between the employment of the two genders. Women are twice as likely to be working part-time and a bit more likely to be working a fixed-term job. They also worked a shorter week on average than men. Of the long-term unemployed 60 % were men. (23)

2.2.2 HEALTH INEQUALITIES IN FINLAND

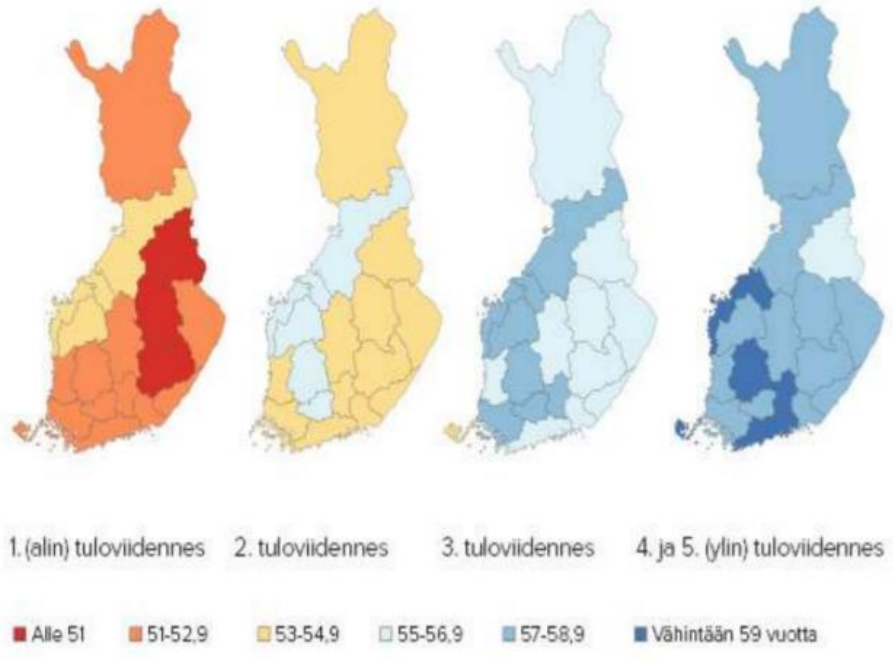
According to recent research the differences in the health of Finnish people are increasing. The biggest factors creating divergence among the Finns are cardiovascular diseases (CVDs) and alcohol-related morbidity. More than 70 % of the regional differences in the mortality of Helsinki metropolitan area could be explained by socioeconomical factors, such as education level, social situation, population density and housing type. There are nationwide regional differences in the health of Finnish people as well. The average lifetime expectancy of a

Finnish new-born is 81,46 years, while in men it ranges from 76.79 to 80.24 and in women from 83,36 to 85,16 depending on the region of birth. (24)

Lower socioeconomic groups did consistently worse than the higher groups in most of the health markers studied in 2014. The lower groups had more detrimental lifestyles; they for example smoked more, ate less vegetables, and exercised less. They also had more trouble with their overall performance, had more long-term illnesses and had lower lifetime expectancy. (25) Moreover, the lower socioeconomic groups had more mental health problems. The most common categories were mood affecting disorders - which was by far the most common one - followed by schizophrenia, schizotypal and delusional disorders. (26)

In figure 2, the differences in lifetime expectancies of 25-year-olds are compared both geographically and by income groups. The picture demonstrates the importance of both factors as for example there are no areas with the lifetime expectancy being less than 51 outside the first income group and on the other hand there are no areas with the lifetime expectancy being at least 59 years outside the fourth- and fifth-income groups. Geographically the maps show the same kinds of patterns across all income groups.

Figure 2: Lifetime expectancy of 25-year-olds in Finland by regions. Data from 2012 – 2014. (27) (In Finnish)



2.2.3 MARKERS OF SOCIOECONOMIS STATUS

As SES consists of multiple factors that affect each other, measuring it is complicated. Most common methods to measure SES are education, occupation, and income. These often correlate positively with each other as higher education level may lead to a higher-class occupation, which again may lead to a better income. The information needed to determine these indicators is relatively easy to gather by questionnaires. (28) Area-based and neighbourhood-level markers are also used when assessing SES. (29)

As a marker of SES, education comprises the immaterial resources of a person, such as knowledge and problem-solving skills. Because education is commonly acquired in young adulthood, it best describes the person's SES in their early life. It can be indicated either as a degree or duration of education. (29) Education can be influenced by family income and parental characteristics. (28) Thus, education is one means, through which SES can be inherited. However, education does not always lead to higher income. (29)

Income is the best indicator for measuring material resources of a person. As money itself does not improve health, the positive effect income can have comes through a wide selection of resources that have a direct impact on an individual's health. Household income is often used instead of individual income, since it better describes the circumstances of everybody living in the household. For the income of different households to be comparable, further information of the households, such as number of people dependant of the income, must be gathered. (14, 28)

Occupation-based measures of SES consider a person's social standing, income, and intellect. They also characterise workplace relations between employers and employees. Most often the longest held or current occupation of a person is used to characterise SES. The measurement does not have to be individual, since for example a measure of "highest status occupation of household" is also used to describe the household as a unit. Perhaps the greatest limitation of occupation-based measurements for SES is that they cannot be applied to people who are unemployed. Most common excluded groups are pensioners, the unemployed, students and people working unpaid, or in informal or illegal jobs. Furthermore, some people are not willing to report their occupation. Also, the classification of different, often even normal but sometimes more unorthodox, professions can be difficult. (28)

2.3 ASSOCIATION OF SOCIOECONOMIC STATUS AND ATHEROSCLEROSIS

2.3.1 SOCIOECONOMIC STATUS AND ATHEROSCLEROSIS RISK FACTORS

Low SES seems to increase the prevalence of multiple atherosclerosis risk factors. Low SES -especially the absence of wealth and low educational level- is a predictor of obesity. SES is associated with a person's risk for obesity, but the relation is not as straightforward as often thought. In the developed societies higher SES generally predicts higher prevalence of obesity in women.

Apart from obesity, poorer dietary choices in the lower SES groups also expose to other atherosclerosis risk factors. (30) Low SES is for instance linked to essential hypertension, which seems to be mainly regulated by sodium intake. Quite predictably, low SES also raises the risk for diabetes. Depending on the SES indicator used, the risk for diabetes is reported to be elevated by 30 to 40 % among those with low SES. The weakest association was found for occupation and diabetes and the strongest one with educational status. The prevalence of diabetes by SES was most consistent amongst women, although it was quite consistent overall. (31) The differences by sex are suggested to be due to the stigmatization of obesity and the social pressure to be thin, which again are both suggested to be stronger among women than men and predominantly among those with high SES. (32) Especially low parental SES is related to increased incidence of diabetes in the offspring. (31)

There are also several studies showing that low SES is associated with greater alcohol consumption and being socially disadvantaged is linked with a risk of being a heavy drinker. Similarly, low SES is also strongly associated with smoking. A higher number of people with low SES are smokers, than those with higher SES. They also seem to smoke more than those who smoke in the higher SES groups. Like in many similar situations, it is suggested that this can be explained by higher SES leading to a higher level of increased knowledge, awareness, and adoption of healthier dietary and other lifestyle patterns. (30)

2.3.2 SOCIOECONOMIC STATUS AND SUBCLINICAL ATHEROSCLEROSIS

Low SES is strongly associated with subclinical atherosclerosis by multiple measures, although there are some vascular markers for which the links are less consistent. The association is greatest among those who most consistently have low SES throughout their lives, and it occurs for multiple indicators of SES - including education, income, and household density during childhood. Individuals with low SES tend to, on average, have

stiffer arteries, increased left ventricular mass, and higher cIMT, which are all markers for CVD. (33)

IMT of individuals is known to be higher in manual workers than in non-manual workers. It is also higher in less educated people than in more educated ones. The association of cIMT and occupation is stronger in Finland than it is in the more Southern Europe. (34) Besides the more presumable association in the adulthood, there is also evidence of a much earlier association between low early-childhood SES and cIMT in mid-childhood, as well as between low childhood SES and adulthood cIMT. (35) Similar results have been obtained comparing childhood SES with carotid plaques. The increase in IMT is likely to be clinically significant as the risk for myocardial infarction increases rapidly as the arterial wall thickens. (36)

In the US, an evident correlation of adulthood SES and cIMT was found in both men and women, as the lowest SES tertile of women had a cIMT of 879.6 μm and in the highest SES tertile the cIMT was 799.5 μm. In men, the corresponding values were 929.30 μm vs. 875.8 μm. The same association, although the difference between the SES groups was not quite as pronounced, was found for childhood SES and cIMT, but not for neighbourhood SES and cIMT. Not every study, however, has indicated a statistically significant association between SES and IMT. For example, in a British study the association between adulthood SES and cIMT was significant in women ($p=0.02$) but not in men ($p=0.33$). (37)

2.3.3 SOCIOECONOMIC STATUS AND CVD MORBIDITY

CVD is a significant factor in the socioeconomic differences in the mortality rates in Europe, as it accounts for 40 % of the socioeconomic differences in the mortality rates among men and 60 % among women. (38). Multiple studies have documented that SES is associated with ischaemic heart disease, stroke and the mortality caused by the diseases. (39) In general, all three of the traditional markers of SES - income, education, and occupation - have a strong association with CVDs in the developed countries. (40) However, of these three markers, occupation had the least consistent association with CVDs, and some studies have found no associations between SES and CVDs. For example, one study found evidence for the association in the UK and northern Europe, but not in France, Switzerland, or the Mediterranean countries. (41)

It has been suggested, that if the prevalence of public health problems was the same across all socioeconomic groups as it is among the highest educated, the mortality caused by CHD would decrease by 45 % (42). In Finland, approximately half of the socioeconomic differences in cardiovascular mortality is explained by higher case fatality, and the other half by higher incidence of myocardial events in the lower socioeconomic groups. (43) Also, growing evidence suggest that prevention and treatment of CVD are not equally shared between socioeconomic groups.

3 AIMS AND HYPOTHESIS OF THE STUDY

3.1 AIMS

The development of atherosclerosis is a life-long process, accelerated by accumulation of risk factors, and young individuals already express signs of subclinical atherosclerosis. SES is evidently associated with cardiovascular health at adult age. However, there is a gap of knowledge whether SES is associated with subclinical markers of atherosclerosis in adolescence and early adulthood. Therefore, the aim of this study was to investigate if early adulthood SES associates with subclinical markers of atherosclerosis since childhood.

3.2 HYPOTHESIS

Prior intervention studies have shown that the presence of risk factors such as dyslipidaemia, obesity, and high blood pressure, predict inferior vascular phenotype beginning from childhood. Likewise, the resolution of the risk factors reduces the risk of cardiovascular events. (7)

As the previous studies have shown, the connection between SES and atherosclerosis is undeniable. The hypothesis of this study is that the association of SES and subclinical markers of atherosclerosis can already be found in adolescence and early adulthood.

4 MATERIALS AND METHODS

4.1 STRIP STUDY

Special Turku Coronary Risk Factor Intervention Project (STRIP) is a randomized and controlled study established at the Research Centre of Applied and Preventive Cardiovascular

Medicine, University of Turku. The study is a continuing dietary intervention trial launched in 1989. (44, 45, figure 3)

Between February 1990 and June 1992, 1062 babies were recruited by well-baby clinic nurses during a 5-month visit. At the Research Centre, the then 7-month-old babies were allocated to either a dietary counselling intervention or control group. Additionally, the STRIP cohort included 2 children with Down syndrome, 2 children with familial hypercholesterolemia, and 5 children who had been randomized into the intervention group but had missed the first study appointments before age 13 months and were later treated as controls. A group of 45 children born between March and July 1989 were also recruited similarly and randomized (intervention group, n = 22; control group, n = 23) to first test the study protocols, thus serving as a "pilot" group. The intervention period continued for 20 years, with concomitant, repeated collection of dietary and cardiovascular health dat. After the 20-year intervention period, the first follow-up was at age 26 years.

Out of the cohort of 1116 individuals, 1072 were invited to participate to the follow-up study visit, and of these, 551 provided follow-up data (51%; intervention group, n = 263; control group, n = 288). More females (n = 308) than males (n = 288) participated in the follow-up. Five of the participants provided only questionnaire data. Attrition analyses have been published previously. In brief, follow-up participants and nonparticipants were similar in terms of dietary components studied, smoking behaviour, physical activity, body mass index, blood pressure, and serum lipid levels. Parental socioeconomic status was similar in the participants and nonparticipants. (46)

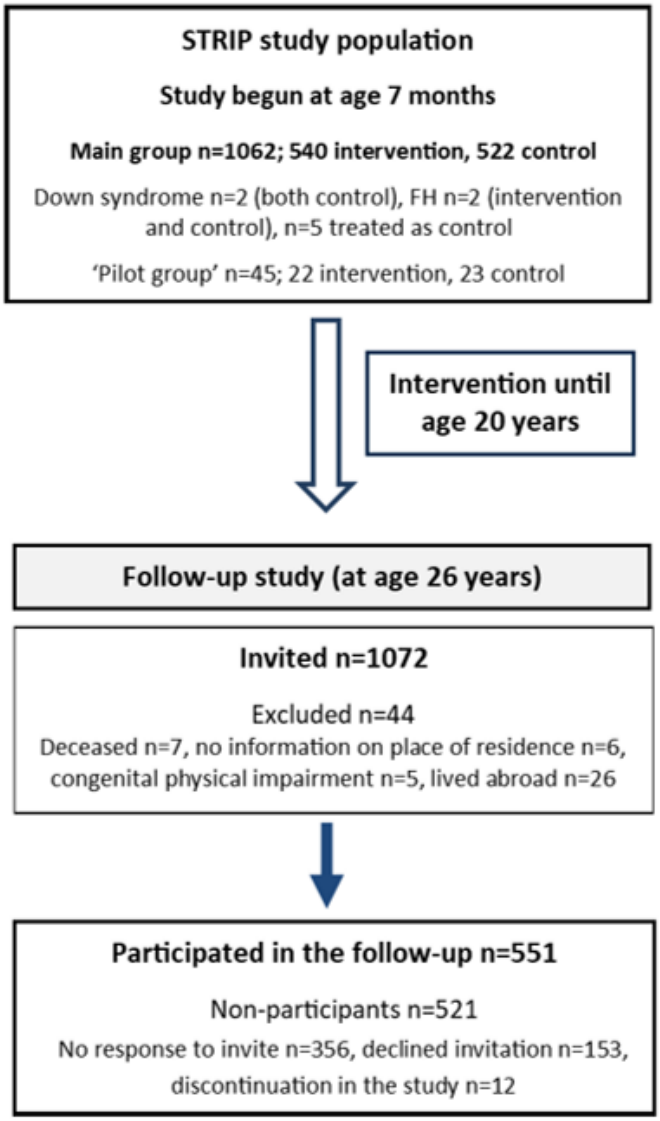


Figure 3 describes the overall study design of the STRIP.

The participants in this study included those for whom data on SES, i.e. profession, at the age of 26 years, and markers of subclinical atherosclerosis [aIMT (aortic intima-media thickness), cIMT (carotid intima-media thickness), plaque] were available.

The study was approved by the ethical authorities of the associated universities and hospital districts. Written informed consent was obtained from parents at study entry and from the participants at age 15, 18 and 26 years. (46)

4.2. STUDY DESIGN AND METHODS

4.2.1 THE GOLDTHORPE CLASS SCHEMA

As a SES classification system, this study used the Goldthorpe class schema. It is also known as the Erikson-Goldthorpe, EGP [Erikson-Goldthorpe-Portocarero and CASMIN (Comparative Study of Social Mobility in Industrial Nations)]. This choice of method was made as the Goldthorpe schema is widely known and used in Finland, and it has performed equally well when compared with other ways to classify SES. (47) It has also been used in other similar studies as the STRIP. The critique it has received is directed toward the schema being more accurate on male-dominated professions than on the female dominated ones. (48) Also, the professions will surely change overtime, meaning that the classification requires constant updating.

The Goldthorpe class schema is based on occupation. It classifies occupations to 11 different groups comprising 7 main groups, 3 of which have subgroups. The groups are designed to merge occupational groups whose members are typically comparable on one hand by the nature of their economic status and on the other hand their autonomy in performing their work tasks. The economic status includes a person's source and level of income, the degree of their economic security and chances of economic advancements. The classification is not a hierarchy; thus it may not capture a gradient in health across the groups. (49, 47)

This study uses a collapsed version of 3-classes due to the relatively limited number of participants. In some cases, information about the participants' educational status was also used to confirm the right occupational classification.

I	Higher grade professionals, administrators and officials; managers in large industrial establishments; large proprietors
II	Lower grade professionals, administrators and officials; higher grade technicians; managers in small industrial establishments; supervisors of non-manual employees
IIIa	Routine non-manual employees, higher grade (administration and commerce)
IIIb	Routine non-manual employees, lower grade (sales and services)
IVa	Small proprietors, artisans and so on, with employees
IVb	Small proprietors, artisans and so on, without employees
IVc	Farmers and small holders; other self-employed workers in primary production
V	Lower grade technicians; supervisors of manual workers
VI	Skilled manual workers
VIIa	Semi-skilled and unskilled manual workers (not in agriculture etc.)
VIIb	Agricultural workers and other workers in primary production

Three-class version	
I–III + IVa + b	Non-manual workers
IVc + VIIb	Farm workers
V + VI + VIIa	Manual workers

Figure 4. Full version of The Goldthorpe class schema, and the three-class collapsed version used in this study. The name of profession group 2 - farm workers- is slightly misleading since it is mostly consisted of workers in primary producion (from group VIIb of full version).

4.2.2 INTIMA-MEDIA THICKNESS OF THE CAROTID AND AORTIC ARTERIES

The vascular ultrasonography studies were performed in silence in a temperature controlled clinical research laboratory. IMT of the common carotid artery and abdominal aorta were assessed using ultrasonography (at age 11 to 19 years: Acuson Sequoia 512; Siemens Healthcare, Mountain View, CA, USA; at age 26 years: GE Vivid E9; GE Vingmend Ultrasound A/S, Horten, Norway) according to standardized protocols. (50, 51, 52) Ultrasound scans were performed by experienced sonographers blinded to participant details.

For the assessment of cIMT, both right and left carotid arteries were scanned with a 15 L 8 linear array transducer at ages 11, 13, 15, 17, and 19 years. The posterior far wall of the common carotid artery was scanned from lateral and anterior oblique angles. The carotid bifurcation was identified, and gain settings were used to optimize image quality so that both the intima of the near and far wall of the common carotid artery 10 to 20 mm proximal to the carotid bifurcation was visible. The resolution box function was used to magnify a 20 mm width image of the common carotid artery far wall and end-diastolic (incident with the R wave on a continuously recorded electrocardiogram) frames were captured and stored for subsequent off-line analysis. At the age of 26 years (follow-up study), right and left common carotid arteries were scanned with an 11 L linear transducer. With the carotid bifurcation identified, the image was focused on the common carotid artery 10 mm proximal to the carotid bifurcation so that both the intima of the near and far wall was visible. A moving scan, including the common carotid artery and the beginning of the carotid bifurcation with a duration of 5 seconds was captured and stored for subsequent off-line analysis. At ages 11, 13, 15, 17, and 19 years, cIMT was measured manually using ultrasonic calipers by readers blinded to participant details. Four cIMT measurements were taken from both lateral and anterior oblique angles on the right and left common carotid artery. The mean value of these IMT measurements was used in statistical analysis. At age 26-years follow-up, cIMT measurements were obtained with a semi-automated TOMTEC AutoIMT (Version TTA2.41.00., TOMTEC Imaging Systems GmbH, Unterschleissheim, Germany) by a single reader blinded to participant details. The best quality end-diastolic (incident with the R wave on a continuously recorded electrocardiogram) frame was selected from the 5-second clip image. On the selected frame, a box approximately 10 mm wide (region of interest) was drawn with TOMTEC 5 to 15 mm proximal to the carotid bifurcation. Then, the program automatically recognized the lumen-intima and media-adventitia boundaries of the far wall, drew lines at the boundaries and automatically calculated the mean IMT for the defined

region of interest. Automated IMT measurements were approved by the reader. If the automatic detection of the arterial boundaries did not work, the reader made three manual IMT measurements. The mean of the right and left cIMT was used for statistical analysis.

For assessing aIMT at ages 11, 13, 15, 17, and 19 years, a linear array transducer 15 L 8 and at age 26 years linear transducer 11 L was used to scan the most distal 15 mm of the abdominal aorta proximal to the bifurcation. A scanning frequency of 13 MHz (12 MHz at age 26 years) was preferred but, when necessary (to reach sufficient tissue penetration), lower scanning frequencies (at the lowest of 8 MHz) were used. At ages 11, 13, 15, 17, and 19, gain settings were used to optimize the image quality and when the intima of the near and far wall was visible the resolution box function was used to magnify a 15 mm width image of the aortic far wall. A frame at end diastole, incident with the R-wave on a continuously recorded electrocardiogram, was captured and stored for subsequent off-line analysis. At age 26 years follow-up, gain settings were used to optimize the image quality and when the intima of the near and far wall was visible, the zoom function was used to magnify a 20 mm width image of the most distal part of the abdominal aorta. A moving clip duration of at least two QRS complexes on a continuously recorded electrocardiogram was captured and stored for subsequent off-line analysis. At ages 11, 13, 15, 17, and 19 years, aIMT was measured by readers blinded to participant details with the use of ultrasonic calipers. Four measurements of IMT covering the entire far wall segment were taken, and the average of these measurements was used. At age 26-years, aIMT was measured by a single reader blinded to participant details. The best quality end-diastolic (incident with the R wave on a continuously recorded electrocardiogram) frame was selected from the moving clip image. On the selected frame, a box (region of interest) was drawn with TOMTEC on the part where the IMT was best visualized. Then, the program automatically recognized the lumen-intima and media-adventitia boundaries of the aortic far wall, drew lines at the boundaries and automatically calculated the mean IMT for the defined region of interest. IMT measurement was then approved by the reader. If the automatic detection of the arterial boundaries did not work, the reader made three manual IMT measurements.

Previously in our laboratory, the between-observer coefficients of variation (CV) of cIMT and aIMT measurements were 3.0% and 3.9%, respectively. And the between-visit CV of cIMT and aIMT measurements were 3.9% and 4.9, respectively.[3] To assess between-observer and between-visit reproducibility of IMT measurements for the 26-year follow-up, we re-examined 50 subjects (~10% random sample) with TOMTEC. The between-observer CV of

IMT measurements was 5.3% for cIMT and 5.7% for aIMT, respectively. The between-visit CV of IMT measurements was 3.8% for cIMT and 5.0% for aIMT, respectively.

4.2.3 CAROTID ARTERY PLAQUE

Carotid ultrasound studies were performed using the GE Vivid E9 ultrasound mainframe (GE Vingmend Ultrasound A/S, Horten, Norway) with an 11 L linear transducer. Participants were examined in supine position with their necks extended. During the ultrasonography, a continuous electrocardiogram was recorded. Ultrasound studies were performed by a single experienced sonographer following to a standardized protocol to assess preclinical markers of atherosclerosis; intima-media thickness (IMT) of the left and right common carotid artery (CCA), carotid bulb, and internal carotid artery (ICA), and left and right CCA, bulb, and ICA carotid atherosclerotic plaques. Throughout the ultrasonography, the sonographer scanned the carotid vascular tree to detect carotid artery plaques, defined as focal structures protruding into the arterial lumen of at least 0.5 mm or 50% of the surrounding IMT value, or demonstrating a thickness of 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface.[1] If carotid plaque was suspected, it was scanned from the longitudinal view so that the plaque-adventitia and plaque-lumen interfaces appeared as accurate as possible. A moving clip with a duration of 5 seconds was then captured and stored for subsequent plaque off-line analysis. IMT measurements and plaque analyses were then performed by a single experienced reader.

4.3 STATISTICAL ANALYSIS

All statistical analyses were performed using SAS version 9.4. and $p < 0.05$ was used to indicate statistical significance. χ^2 test was used to investigate sex difference in the profession groups at age 26 years. Associations of the profession group with aIMT, cIMT and plaque were studied with a linear mixed effects model for repeated measures using compound symmetry covariance structure. All models included age and sex as covariates.

5 RESULTS

At age 11 years, 252 participants were eligible to this study. Their mean BMI was 17.5 kg/m^2, mean waist circumference 63.0 cm, mean systolic blood pressure 105 mmHg, and mean serum total cholesterol concentration was 4.5 mmol/L. At the age of 26 years, 355 participants had eligible data. Their mean BMI was 24.7 kg/m^2, mean waist circumference 81.3 cm, mean systolic blood pressure 121 mmHg, and their mean plasma total cholesterol concentration was 4.6 mmol/L.

Table 1. Characteristic of the participant at the age of 11 and 26 years.

	Age 11 years			**Age 26 years**		
Characteristics	**N**	**Mean**	**std**	**N**	**Mean**	**std**
BMI (kg/m^2)	252	17.5	2.7	354	24.7	4.3
Waist (cm)	246	63.0	7.4	354	81.3	10.8
Systolic blood pressure (mmHg)	252	105.7	9.1	354	121.3	10.6
Diastolic blood pressure (mmHg)	252	58.5	6.1	354	71.6	7.2
Serum total cholesterol (mmol/L)	248	4.5	0.8	353	4.6	0.9
Serum HDL-cholesterol (mmol/L)	248	1.3	0.3	353	1.3	0.3
Serum LDL-cholesterol (mmol/L)	248	2.8	0.7	353	2.8	0.75
Serum triglycerides (mmol/L)	248	0.8	0.5	353	1.0	0.43

Of the participants who provided data on their profession at age 26 years (n=355), 56.6% (n=201) were female. Females were more likely to be in the highest SES group compared with men (p=0.0062). The first SES group had the most participants, but overall the distribution was relatively even.

Table 2. Distribution of sexes (%, n) between the profession groups. (1=non-manual workers, 2=farm workers/primary production, 3=manual workers)

	Profession group			
	1 (highest)	**2**	**3 (lowest)**	**Total**
Females, % (n)	65.4 (85)	57.8 (67)	45.0 (49)	56.6 (201)
Males, % (n)	34.6 (45)	42.2 (49)	55.1 (60)	43.4 (154)

Tables 3-4 describe the mean aIMT and cIMT between ages 11 and 26 years in the profession groups.

Table 3. Mean aIMT (mm) between ages 11 and 26 years in the profession groups (1=non-manual workers, 2=farm workers/primary production, 3=manual workers).

Profession group	**1**		**2**		**3**	
Age (years)	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
11	0.51	0.06	0.50	0.08	0.53	0.07
13	0.52	0.12	0.51	0.08	0.54	0.14
15	0.51	0.08	0.52	0.09	0.53	0.09
17	0.54	0.10	0.51	0.11	0.52	0.10
19	0.51	0.10	0.52	0.09	0.51	0.11
26	0.62	0.16	0.62	0.15	0.61	0.14

Table 4. Mean cIMT (mm) between ages 11 and 26 years in the profession groups (1=non-manual workers, 2=farm workers/primary production, 3=manual workers).

Profession group	**1**		**2**		**3**	
Age	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
11	0.46	0.04	0.45	0.05	0.47	0.05
13	0.45	0.06	0.44	0.06	0.44	0.05
15	0.45	0.05	0.45	0.04	0.46	0.04
17	0.42	0.06	0.41	0.06	0.44	0.05
19	0.40	0.04	0.41	0.04	0.40	0.04
26	0.46	0.06	0.46	0.06	0.45	0.05

There was no association between the profession groups in either aIMT (p=0.79) or cIMT (p=0.33) between the ages of 11 and 26 years (adjusted for age and sex; Tables 3-4 and Figures 5 and 6). These results remained after the analyses were further adjusted for BMI and systolic blood pressure.

Figure 5: aIMT between ages 11 and 26 years by profession groups. (1=non-manual workers, 2=farm workers/primary production, 3=manual workers).

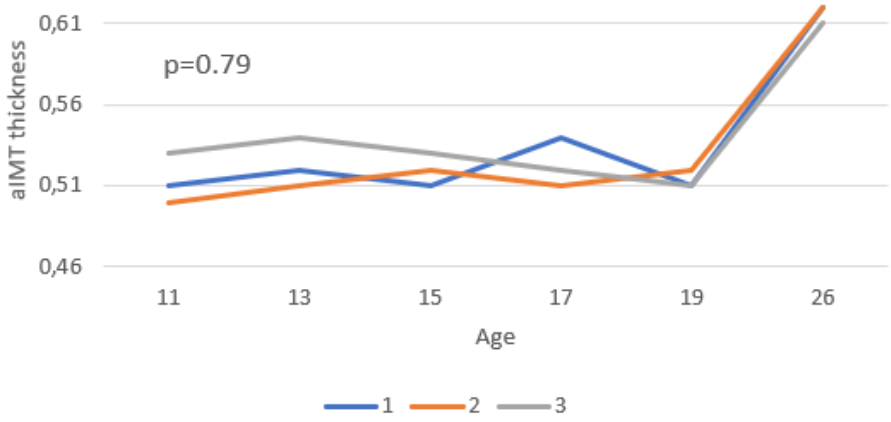
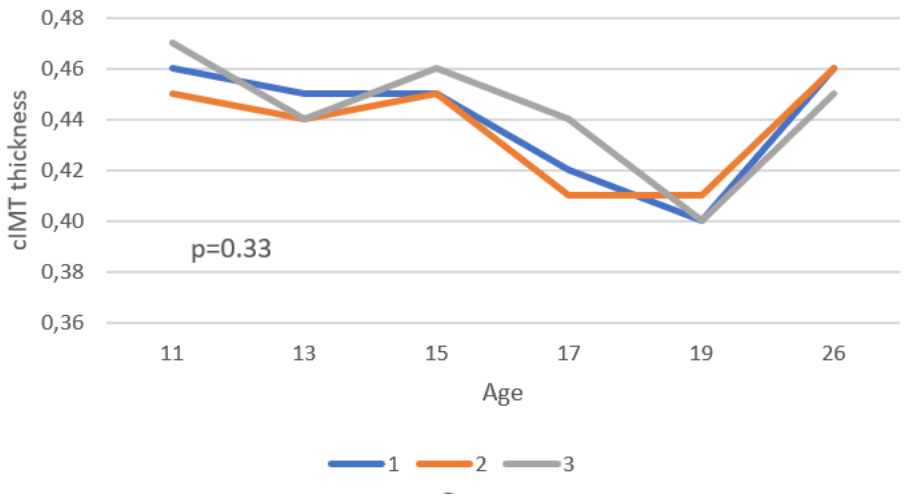


Figure 6: cIMT between ages 11 and 26 years by profession groups. (1=non-manual workers, 2=farm workers/primary production, 3=manual workers).



Of the participants in this sub-cohort, 6.1 % had a carotid artery plaque. The profession group was not associated with having a carotid artery plaque (group 1: 7.3 %, group 2: 5.2 %, group 3: 5.5. %; p=0.55 (Cochran-Mantel-Haenszel statistics).

Table 5. Frequency of plaque in different profession groups.

Profession group	**1**	**2**	**3**	**Total**
Frequency of a plaque	7.3%	5.2%	5.5%	6.1%

6 DISCUSSION AND CONCLUSIONS

The results indicate that SES defined by profession in early adulthood is not associated with subclinical markers of atherosclerosis assessed between ages 11 and 26 years. These results are in contrast with similar studies, comprising older participants. (33, 53) Studies conducted in older participants have indicated that low SES increases the risk for a disease driven by an atherosclerotic process. (39) However, as there are no prior studies investigating the association of SES and subclinical markers of atherosclerosis beginning from childhood, comparison to prior studies is hampered.

The contrast may be due to the young age of the participants, i.e., the atherosclerotic process has not had enough time to develop. Another reason may be that the participants have had their current SES only for a little time, and some have not yet reached the SES they will eventually settle for. Of the participants, 7% were students, most of whom will not settle for the socioeconomic group they are at now. While the applied SES classification may create inaccuracy to the results – a weakness shared by all SES-classification procedures - the longitudinal in vivo assessment of vascular health via ultrasonography is a definite strength of the study.

Cardiovascular health consists of multiple factors, one of which is SES. In a study that considered 7 factors of ideal cardiovascular health (none of which was SES), it was found, that the more beneficial factors the participants had, the lower their IMT was, and vice versa.

(54) Perhaps the effect SES has on cardiovascular health, is yet overshadowed by other more significant factors in early adulthood.

Other similar studies applying longitudinal imagining data on vascular health since childhood – and perhaps also using diverse indicators of SES – would be valuable to confirm, or contrast, the results shown by this study.

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