



HAL
open science

Associations of childhood adiposity with adult intima–media thickness and inflammation: a 20-year longitudinal population-based cohort

Tomona Fujikawa, Masatake Kobayashi, Sandra Wagner, Kevin Duarte, Pauline Scherdel, Barbara Heude, Vincent Dupont, Erwan Bozec, Emmanuel Bresso, Faiez Zannad, et al.

► To cite this version:

Tomona Fujikawa, Masatake Kobayashi, Sandra Wagner, Kevin Duarte, Pauline Scherdel, et al.. Associations of childhood adiposity with adult intima–media thickness and inflammation: a 20-year longitudinal population-based cohort. *Journal of Hypertension*, 2023, 41 (3), pp.402-410. 10.1097/HJH.0000000000003343 . hal-04097408

HAL Id: hal-04097408

<https://hal.univ-lorraine.fr/hal-04097408v1>

Submitted on 15 May 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Associations of Childhood Adiposity with Adult Intima Media Thickness and Inflammation: A 20-Year Longitudinal Population-based Cohort

Running title: Childhood adiposity, adult carotid IMT and inflammation

Tomona Fujikawa*¹, Masatake Kobayashi*¹, Sandra Wagner¹, Kevin Duarte¹, Pauline Scherdel², Barbara Heude², Vincent Dupont^{3,4}, Erwan Bozec¹, Emmanuel Bresso¹, Faiez Zannad¹, Patrick Rossignol¹, Nicolas Girerd¹

* co-first authors

1. Université de Lorraine, Centre d'Investigations Cliniques Plurithématique 1433, INSERM 1116, CHRU de Nancy, France; F-CRIN INI-CRCT Cardiovascular and Renal Clinical Trialists Network, France.
2. INSERM, UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), Early determinants of the child's health and development Team (ORCHAD), Paris, France, Paris Descartes University, France.
3. Département de Néphrologie, Centre Hospitalier Universitaire de Reims, Reims, France.
4. French Clinical Research Infrastructure Network, Investigation Network Initiative - Cardiovascular and Renal Clinical Trialists (F-CRIN INI-CRCT), Reims, France.

Corresponding Author:

Pr. Nicolas Girerd

Centre d'Investigation Clinique Pierre Drouin -INSERM - CHRU de Nancy, Institut lorrain du coeur et des vaisseaux Louis Mathieu, Nancy, France

Address: 4, rue du Morvan. 54500 Vandoeuvre-Les-Nancy

E-mail: n.girerd@chru-nancy.fr Phone: +33383157496 Fax: +33383157324

Tables and figures: 2 tables and 2 figures

Funding:

The STANISLAS Cohort visit 4 is sponsored by the Nancy CHRU and is funded in part by the Programme Hospitalier de Recherche Clinique Interrégional. Biomarker studies are co-funded by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004) and FEDER Lorraine, and all French co-authors are supported by the French PIA project "Lorraine Université d'Excellence" GEENAGE (ANR-15-IDEX-04-LUE) programs, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP. The research leading to these results has also received funding from the European Union Commission's Seventh Framework program under grant agreement No. 305507 (HOMAGE). We also acknowledge support from the "EXPERT" ERA-CVD 2016 and MR-Focus (both grants managed by the French National Research Agency).

Acknowledgments:

We are highly grateful to the *Vandoeuvre-Lès Nancy Centre de Médecine Préventive* staff, and to Dr Sophie Visvikis-Siest (Inserm U1122) who managed the STANISLAS Cohort for the first three visits.

The authors warmly thank the Staff of the Clinical Investigation Center and other personnel

involved in the STANISLAS Cohort management: Biostatisticians: Fay R, Lamiral Z, Machu JL. Computer scientists: Boucenna N, Gallina-Muller C, Maclot PL, Sas T. Co-investigators: Chau K, Di Patrizio P, Dobre D, Gonthier D, Huttin O, Malingrey L, Mauffrey V, Olivier A, Poyeton T, Steyer E, Watfa G. Datamanagers: Cimon P, Eby E, Merckle L. Data entry operators: Batsh M, Blanger O, Bottelin C, Haskour N, Jacquet V, Przybylski MC, Saribekyan Y, Thomas H, Vallee M. Echocardiographers, echographers: Ben Sassi M, Cario S, Camara Y, Coiro S, Frikha Z, Kearney-Schwartz A, Selton-Suty C, Watfa G. Imaging engineer: Bozec E. Laboratory Engineer Nuee-Capiaumont J and Technicians: Fruminet J, Kuntz M, Ravey J, Rousseau E, Tachet C. Project managers: Bouali S, Hertz C. Quality engineer: Lepage X. Registered nurses: Giansily M, Poinsignon L, Robin N, Schmartz M, Senn M, Micor-Patrignani E, Toutlemonde M. Hospital technician: Fleurot MT. Resident physicians: Alvarez- Vasquez R, Amiot M, Angotti M, Babel E, Balland M, Bannay A, Basselin P, Benoit P, Bercand J, Bouazzi M, Boubel E, Boucherab- Brik N, Boyer F, Champagne C, Chenna SA, Clochey J, Czolnowski D, Dal-Pozzolo J, Desse L, Donetti B, Dugelay G, Friang C, Galante M, Garel M, Gellenoncourt A, Guillin A, Hariton ML, Hinsiger M, Haudiquet E, Hubert JM, Hurtaud A, Jabbour J, Jeckel S, Kecha A, Kelche G, Kieffert C, Laurie`re E, Legay M, Mansuy A, Millet-Muresan O, Meyer N, Mourton E, Naude`AL, Pikus AC, Poucher M, Prot M, Quartino A, Saintot M, Schiavi A, Schumman R, Serot M, Sert C, Siboescu R, Terrier-de-la-Chaise S, Thiesse A, Thietry L, Vanesson M, Viellard M. Secretaries: De Amornin E, Villemain C, Ziegler N. Study Coordinators: Dauchy E, Laurent S, and all persons not listed above who helped in the funding, initiation, accrual, management and analysis of the fourth visit of the STANISLAS cohort. The authors also thank the Nancy CHRU CRB Lorraine for its management of the biobank. Steering committee: Pierre Mutzenhardt, Mehdy Siaghy, Patrick Lacolley, Marie-Ange Luc, Pierre-Yves Marie, Jean-Michel Vignaud. Advisory members: Sophie Visvikis Siest, Faiez Zannad. Technical committee: Christiane Branlant, Isabelle Behm-Ansmant, Jean-Michel Vignaud, Christophe Philippe, Jacques Magdalou, Faiez Zannad, Patrick Rossignol. Scientific committee: Laurence Tiret, Denis Wahl, Athanase Benetos, Javier Diez, Maurizio Ferrari, Jean-Louis Gueant, Georges Dedoussis, François Alla, François Gueyffier, Pierre-Yves Scarabin, Claire Bonithon Kopp, Xavier Jouven, Jean-Claude Voegel, Jan Staessen.

The Knut and Alice Wallenberg Foundation is also acknowledged for its generous support.

Conflict of interest:

NG, PR and FZ are supported by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004), by the French PIA project Lorraine Université d'Excellence GEENAGE (ANR-15-IDEX-04-LUE) programs, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP. NG received consulting fees from Novartis, AstraZeneca and Boehringer. PR reports grants and personal fees from AstraZeneca, Bayer, CVRx, Fresenius, and Novartis, personal fees from Grunenthal, Servier, Stealth Peptides, Vifor Fresenius Medical Care Renal Pharma, Idorsia, NovoNordisk, Ablative Solutions, G3P, Corvidia, Relypsa. FZ reports personal fees from Boehringer Ingelheim; personal fees from Janssen, Novartis, Boston Scientific, Amgen, CVRx, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmaceutical, Applied Therapeutics, Merck, Bayer and Cellprothera outside the submitted work; and other support from CVCT and Cardiorenal, outside the submitted work. JPF has received consulting fees from Boehringer Ingelheim. All other authors report no conflicts of interest with regard to this article.

Abstract

Background

The associations between childhood adiposity and adult increased carotid intima thickness (cIMT) have been well-established, which might be corroborated by the association between adiposity in children and inflammation in adults. However, longitudinal data regarding biological pathways associated with childhood adiposity are lacking.

Methods

The present study included participants from the STANISLAS cohort who had adiposity measurements at age 5-18 years (N=519, mean [SD] age, 13.0 [2.9] years; 46.4% male), and who were measured with cIMT, vascular- and metabolic-related proteins at a median follow-up of 19±2 years. Body mass index (BMI), waist-to-height ratio and waist circumference were converted to age- and sex-specific z-scores.

Results

A minority of children were overweight/obese (16.2% overweight-BMI z-score>1; 1.3% obesity-z-score>2). Higher BMI, waist-height ratio and waist circumference in children were significantly associated with greater adult cIMT in univariable analysis, although not after adjusting for C-reactive protein (CRP). These associations were more pronounced in those with consistently high adiposity status from childhood to middle-adulthood. Participants with higher adiposity during childhood (BMI or waist-height ratio) had higher levels of insulin-like growth factor binding protein-1, and -2, matrix metalloproteinase-3, osteopontin, hemoglobin and CRP at adulthood. Network analysis showed that interleukin-6, insulin-like growth factor-1 and fibronectin were the key proteins associated with childhood adiposity.

Conclusions

In a population-based cohort followed for 20 years, higher BMI or waist-to-height ratio in childhood was significantly associated with greater cIMT and enhanced levels of proteins reflective of inflammation, supporting the importance of inflammation as the progressive atherosclerosis in childhood adiposity.

Keywords: childhood adiposity, carotid intima media thickness, biomarkers, inflammation.

Introduction

The prevalence of overweight and obesity has substantially increased in children over the last decades¹. Large epidemiological studies have established that a high childhood adiposity status is associated with a risk of increased carotid intima media thickness (cIMT) in mid-adulthood^{2,3}. However, given that childhood adiposity is highly related to adult adiposity, the attributable risk specific to childhood adiposity is difficult to quantify. Hence, the assessment of trajectories of child-to-adult adiposity may better discriminate the relative impact of childhood and/or adult adiposity status on adult increased cIMT.

The underlying mechanisms in adults associated with childhood adiposity might underpin the associations between childhood adiposity and adult increased cIMT. Inflammation is related to adiposity and atherosclerotic disease but the interplay between these 3 features (adiposity, atherosclerotic disease, and inflammation) were predominantly studied in cross-sectional studies⁴⁻⁶. Longitudinal data whether children with adiposity status were prone to have heightened inflammation status in adults are lacking. An approach to better understand biological pathways is to use knowledge-based network analysis on the results retrieved by circulating protein analysis. This approach may help better understand which circulating proteins may be pivotal of these protein-protein relationships^{7,8}.

In the STANISLAS (Suivi Temporaire Annuel Non-Invasif de la Santé des Lorrains Assurés Sociaux) cohort followed over 20 years, circulating proteins of various pathophysiological pathways were collected⁹. In the present study, we aimed at exploring: 1) the association between childhood adiposity and adult cIMT as well as circulating proteins expressing vasculature and adiposity, 2) the associations of child-to-adult adiposity trajectories with adult cIMT, and 3) identifying the biological pathways underlying the association between childhood adiposity and adult vascular alterations.

Methods

Study population

The STANISLAS cohort is a single-center familial longitudinal cohort from the Nancy region in France, the features of which have been previously described ¹⁰. Among 4,295 participants undergoing the 1st cohort visit from 1993 to 1995, 519 children aged 5 to 18 years with available data on vascular variables at the 4th visit (from 2011 to 2016) were included in the current analysis (*Supplemental Figure 1*). The study was approved by the Ethics Committee (Comité de Protection des Personnes Est III, Nancy, France), and all study participants gave their written informed consent to participate (ClinicalTrials.gov identifier NCT01391442).

All participants completed medical and socio-demographic questionnaires, and underwent a physical examination and vascular measurements. Collected variables included age, sex, height, weight, smoking status and physical activity. Standard biochemical blood parameters included triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, blood glucose, glycated hemoglobin and estimated glomerular filtration rate (eGFR, as calculated from the Schwartz formula in children ¹¹, and the Chronic Kidney Disease Epidemiology Collaboration formula in adults ¹²). Metabolic syndrome in adults was defined according to Adult Treatment Panel III criteria ¹³.

Body mass index, waist circumference and waist-to-height ratio

BMI was calculated by weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the narrowest level, and waist-to-height ratio was calculated from the ratio of waist circumference and height. Body mass index (BMI) was converted to age- and sex-specific z score based on the International Obesity Task Force (IOTF)¹⁴, while waist-to-height ratio and waist circumference were based on the Third National Health and Nutrition Examination Survey (NHANES III) ¹⁵. Overweight and obesity

were respectively defined by a BMI z-score >1 and >2 as proposed by the IOTF¹⁶.

Vascular variables

cIMT was measured by high-resolution echo-tracking in a controlled environment at $22\pm 1^\circ\text{C}$ after 10 min of rest in the supine position. Carotid diameter, distension and intima media thickness were measured on the right common carotid artery¹⁷. Examinations were successively performed with the wall track system (WTS, ESAOTE, Maastricht, The Netherlands) and the ART.LAB (ESAOTE, Maastricht, The Netherlands). The detailed methodology and excellent reproducibility of cIMT measurements in this cohort has previously been reported¹⁸.

Circulating proteins

For vascular-related biomarkers, extracellular matrix remodeling in vasculature, angiogenesis and endothelial cell dysfunction were supported by the expression of matrix metalloproteinase-2 (MMP-2), MMP-3, MMP-9, vascular endothelial growth factor A (VEGF-A), bone morphogenetic protein-9 (BMP-9), insulin-like growth factor binding protein-1 (IGFBP-1), IGFBP-2, osteopontin (OPN) and Cystatin C¹⁹⁻²⁶. For adiposity-related biomarkers, fatty acid-binding protein-4 (FABP-4), leptin, resistin, cystatin C, kidney injury molecule-1 (KIM-1), hemoglobin, interferon-gamma (IFN- γ), C-reactive protein (CRP), triglycerides were also studied²⁷⁻²⁹. These selected biomarkers were measured using Olink Proseek® Multiplex cardiometabolic, cardiovascular II, III and Inflammation 96x96 kits in serum using proximity extension assay technology (<https://www.olink.com/products/complete-protein-biomarkers-list>)³⁰.

Complex network analysis

The Fight-HF graph knowledge box was used to build the complex network⁷. Direct interaction between studied biomarkers were extracted from the STRING database³¹. The other proteins known to directly interact with at least five biomarkers were added to the

network. Biomarkers belonging to the same REACTOME pathway were linked as indirect interaction³².

Statistical analysis

Categorical variables are presented as frequencies (percentages) and continuous variables as means \pm standard deviation or median (25th and 75th percentiles) depending on variable distribution. Comparisons of demographic, clinical and biological variables according to tertiles of childhood adiposity status were analyzed using ANOVA, Kruskal-Wallis test and χ^2 test, as appropriate.

Linear regression analyses were used to study the associations of childhood adiposity as assessed by BMI, waist-height ratio, and waist-circumference with adult vascular variables. These models were adjusted for clinical variables specific for the childhood and adult periods, respectively: childhood model – age, sex, systolic blood pressure (BP), blood glucose, total cholesterol, triglycerides and natural log of C-reactive protein (CRP); adult model – age, sex, prevalence of metabolic syndrome³³, hypertension, systolic BP, diastolic BP, total cholesterol and triglycerides.

To assess whether the biomarkers were expressed differently between children with higher (top tertile) and lower (bottom tertile) BMI or waist-height ratio, multinomial logistic regression analyses were performed after adjustment for respective BMI or waist-height ratio in adults as an independent variable plus age, a prevalence of metabolic syndrome, hypertension, diabetes mellitus, systolic BP and total cholesterol.

All analyses were performed using R version 4.0.1 (R Development Core Team, Vienna, Austria). A two-sided p-value <0.05 was considered statistically significant.

Results

Baseline characteristics according to childhood adiposity

Among the 519 children included in this study, slightly less than a half were males

(46.4%), mean age (SD) was 13.0 (2.9) years, 38.7% (N=201) were adolescents (≥ 14 years), mean BMI z-score was 0.04 (0.90) (16.2% overweight, 1.3% obesity) and the median follow-up period was 19.1 years (25th and 75th centiles 17.9 to 20.0).

Children with higher age- and sex-standardized BMI had higher CRP levels at childhood, and more frequent prevalence of metabolic syndrome at adulthood (all-p-values < 0.05) (*Table 1*). Children with higher age- and sex-standardized waist-height ratio were male, had higher blood pressure, lower heart rates, greater inflammation status at childhood, higher BP and cIMT at adulthood (*Table 1*).

Baseline characteristics according to the tertiles of age- and sex-standardized waist circumference are presented in *Supplemental Table 1*. Baseline characteristics associated with waist circumference were similar to those associated with waist-to-height ratio.

Associations between childhood adiposity and adult intima media thickness

In univariable models, high childhood adiposity status as assessed by higher BMI, waist-height ratio and waist circumference was significantly and consistently associated with greater cIMT at adulthood. These associations persisted after adjustment for clinical covariates measured at both childhood and adult periods. However, after adjustment for covariates including CRP measured at childhood, these associations no longer remained significant (all p-values > 0.05) (*Table 2*).

The observed associations between childhood adiposity status and adult cIMT were similar in adolescents (≥ 14 years) and children (< 14 years) (all-P for interaction > 0.10), whereas the associations between childhood adiposity status and cIMT were prominent in females (all-P for interaction < 0.01) (*Supplemental Table 2*).

The association of overweight or obesity in children with adult cIMT was not modified by CRP levels in children (P-value > 0.10).

Association between child-to-adult adiposity trajectories and adult intima media

thickness

Subjects were divided into 4 categories according to a median value of childhood and adult adiposity (*i.e.*, BMI, waist-to-height ratio and waist circumference). Subjects with consistently high BMI from childhood to middle adulthood were likely to have a greater cIMT than those who had low BMI in both periods, with these associations persisting after adjustment for potential confounders (*Figure 1 & Supplemental Table 3*). In addition, subjects who had a high waist-to-height ratio as adults, irrespective of their childhood waist-to-height ratio, were likely to have greater cIMT, with these associations also remaining significant even in multivariable models (*Figure 1 & Supplemental Table 3*).

Complex network analysis

IGFBP-1, IGFBP-2, MMP-3, osteoponin, hemoglobin and CRP levels were significantly higher (up-regulated), whereas VEGF-A, FABP-4, leptin, and IFN-gamma were significantly lower (down-regulated) in individuals with higher childhood adiposity status (based on BMI or waist-height ratio) (*Supplemental Table 4*). Among these proteins associated with childhood adiposity, interleukin-6 (IL-6), insulin-like growth factor-1 (IGF-1) and fibronectin were the pivotal proteins linked to 5 proteins. *Figure 2*.

Discussion

In the present French population-based cohort followed over a period of 20 years, a higher adiposity status as assessed by higher BMI, waist-height ratio or waist circumference in childhood was found to be consistently and independently associated with greater cIMT in adulthood, although these associations no longer remained significant after adjusting for inflammation (as assessed by CRP at childhood). In addition, subjects with consistently high BMI from childhood to adulthood were likely to have greater cIMT in adulthood. Inflammation, as expressed by IL-6 and IGF-1, may possibly represent central proteins associated with childhood

adiposity.

Taken together, these data point to the potential relevance of inflammatory-related pathways in explaining the associations between childhood adiposity and middle-age atherosclerosis.

Associations between childhood adiposity and adult cIMT

In the present study, the proportions of overweight and obese children were similar to those documented in previous reports^{34,35}. Childhood adiposity as assessed by higher BMI, waist-height-ratio or waist circumference was associated with greater cIMT in middle-aged adults^{2,3,36,37}. Furthermore, subjects with consistently high BMI from childhood to adulthood were likely to have greater cIMT in adults, which are consistent with previous reports^{3,36}. By contrast, higher waist-to-height ratio in adults rather than children was associated with greater adult cIMT. These findings suggest that waist circumference may less likely express adiposity status particularly in children, and that assessing childhood abdominal fat may be less reliable to predict the degree of adult cIMT. Interestingly, although physiological studies show overweight or obese individuals have higher or similar heart rate than lean ones, in the current analysis, higher waist circumference was associated with lower heart rate. As, in prior studies, body weight and height-based measurements (*i.e.*, BMI) were used to define overweight or obesity^{38,39}. This may have an impact on the results as larger height has been shown to be associated with lower heart rate⁴⁰, which may counterbalance the differences in heart rate among BMI tertile groups.

Of note, the association between childhood adiposity status and adult increased cIMT was more pronounced in females than in males, which may be partly explained by the substantial sex-related differences in the adipose distribution^{41,42}. Women are likely to have greater peripheral fat depots and lower skeletal muscle mass, while men are likely to have greater central adiposity and higher skeletal muscle mass. Although prior longitudinal data was consistent with our results⁴³, such sex-related differences are modified by several

environmental factors (i.e., diet, physical activity), and further data are required to rigorously evaluate these sex-related interactions. Of further interest, all observed associations between childhood adiposity status and adult cIMT lost their statistical significance when CRP was included in the multivariable models. Although, among middle-aged adults, our team reported that adiposity was an important predictor of long-term increases in pulse wave velocity, independent of inflammation status⁴⁴, the current findings may highlight that adiposity status in children induces an inflammation state, which may be involved in atherosclerotic progression^{45, 46}. Our observations, therefore, suggest that inflammation may be a key biological factor underlying the association between childhood adiposity status and adult cIMT.

Inflammation markers as central proteins associated with childhood adiposity

A growing number of papers use many circulating proteins resulting in many relevant associations. Filtration and/or integration of these associations, therefore, should be required to better interpret the results. In this regard, network analysis is becoming a relevant step of omics-based analyses to better demonstrate protein, disease, and pathway relations.

Our network analysis demonstrated that childhood adiposity was associated with inflammatory response over 20 years, which was mainly mediated by IL-6 and IGF-1 in the network analysis. IL-6 is a well-known cytokine involved in the regulation of the inflammation and immune response⁴⁷. IL-6 and interleukin-1 β as a driver of IL-6, play important roles on progressive atherosclerosis such as the development of atherothrombotic plaque, the advancement of monocyte/leukocyte adhesion to vascular endothelial cells, and the progress of vascular smooth-muscle cells^{48,49}. Prior reports showed higher IL-6 levels were associated with greater degrees of cIMT in population settings^{50, 51}. IGF-1 is also known as a mediator of inflammation response, and its excess induces pro-inflammatory cytokine production, may promote endothelial dysfunction, and increase oxidative stress, possibly contributing to the

progression of atherosclerosis^{52,53}. Fibronectin, another central protein in our network, may represent a link between inflammation and vascular remodeling: Budatha and colleagues reported that fibronectin and integrin $\alpha 5$ signaling are key elements of pathological vascular remodeling in hypertension models⁵⁴. Fibronectin in injured, remodeled, or inflamed vessels, could sensitize endothelial cells to inflammation through integrins upregulation⁵⁴.

Taken together, these findings highlighted that childhood adiposity was associated with inflammatory-related process in adults, irrespective of adult adiposity status, and that inflammation, supported by fibronectin sensitization, may be a key determinant of progressing atherosclerosis as evaluated by cIMT.

Clinical perspectives

Increased cIMT is associated with a high risk of future development of atherosclerotic diseases such as stroke and/or coronary artery disease^{55, 56}. Our results consequently suggest that childhood adiposity is associated with deleterious long-term vascular evolution. From a prevention perspective, assessing childhood adiposity status and subsequently implementing interventions toward weight reduction should therefore be promoted, as already emphasized in several studies^{3, 36}.

Our findings emphasize the importance of inflammation pathway in the link between childhood adiposity and adult atherosclerotic disease. Indeed, the conjunction of adiposity and inflammation, possibly related to visceral obesity, appears as a potent vector of long-term vascular impairment⁵⁷.

Recently published data showed that, canakinumab, as anti-inflammatory agents for Il-6 cytokine, diminished atherosclerotic progression in an experimental animal study⁵⁸. Moreover, this treatment significantly reduced rate of recurrent cardiovascular events (*i.e.*, myocardial infarction, stroke, or cardiovascular death), compared with placebo, independent of lipid-level lowering agents⁵⁹. Further studies, therefore, should be required to test the effects of canakinumab on alterations in

intima media thickness, particularly in people who had a childhood adiposity status, in light of our results.

Limitations

Our results should be interpreted in light of the following limitations. This study is limited by its inherent observational design; thus, causality cannot be inferred. The proportions of overweight and obese children were relatively small, although these proportions were similar to those in previous reports^{34, 35}. Waist-to-height ratio and waist circumference were converted to age- and sex-specific z scores based on the NHANES III, which is often applied to children in the US¹⁵. Nevertheless, we observed similar associations of BMI, waist-to-height ratio and waist circumference, suggesting that different scales may have less of an impact on the observed associations between childhood adiposity and adult vascular alterations. In addition, no data were available regarding vascular-related proteins measured in the childhood period. Further study is warranted to externally validate our findings in other community-based cohorts.

Conclusions

In a population-based cohort followed for 20 years, higher BMI or waist-to-height ratio in childhood was significantly associated with greater cIMT and enhanced levels of proteins reflective of inflammation, supporting the importance of inflammation as the progressive atherosclerosis in childhood adiposity.

References

1. Wang Y and Lobstein T. Worldwide trends in childhood overweight and obesity. *International journal of pediatric obesity : IJPO : an official journal of the International Association for the Study of Obesity*. 2006;1:11-25.
2. Koskinen J, Kähönen M, Viikari JS, Taittonen L, Laitinen T, Rönnemaa T, Lehtimäki

T, Hutri-Kähönen N, Pietikäinen M, Jokinen E, Helenius H, Mattsson N, Raitakari OT and Juonala M. Conventional cardiovascular risk factors and metabolic syndrome in predicting carotid intima-media thickness progression in young adults: the cardiovascular risk in young Finns study. *Circulation*. 2009;120:229-36.

3. Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, Srinivasan SR, Daniels SR, Davis PH, Chen W, Sun C, Cheung M, Viikari JS, Dwyer T and Raitakari OT. Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med*. 2011;365:1876-85.

4. Rocha VZ and Libby P. Obesity, inflammation, and atherosclerosis. *Nature reviews Cardiology*. 2009;6:399-409.

5. Kotsis VT, Stabouli SV, Papamichael CM and Zakopoulos NA. Impact of obesity in intima media thickness of carotid arteries. *Obesity (Silver Spring, Md)*. 2006;14:1708-15.

6. Stabouli S, Kotsis V, Papamichael C, Constantopoulos A and Zakopoulos N. Adolescent obesity is associated with high ambulatory blood pressure and increased carotid intimal-medial thickness. *The Journal of pediatrics*. 2005;147:651-6.

7. Girerd N, Bresso E, Devignes MD and Rossignol P. Insulin-like growth factor binding protein 2: A prognostic biomarker for heart failure hardly redundant with natriuretic peptides. *International journal of cardiology*. 2020;300:252-254.

8. Ferreira JP, Verdonschot J, Wang P, Pizard A, Collier T, Ahmed FZ, Brunner-La-Rocca HP, Clark AL, Cosmi F, Cuthbert J, Díez J, Edelmann F, Girerd N, González A, Grojean S, Hazebroek M, Khan J, Latini R, Mamas MA, Mariottoni B, Mujaj B, Pellicori P, Petutschnigg J, Pieske B, Rossignol P, Rouet P, Staessen JA, Cleland JGF, Heymans S and Zannad F. Proteomic and Mechanistic Analysis of Spironolactone in Patients at Risk for HF. *JACC Heart Fail*. 2021;9:268-277.

9. Ferreira JP, Girerd N, Bozec E, Merckle L, Pizard A, Bouali S, Eby E, Leroy C,

Machu JL, Boivin JM, Lamiral Z, Rossignol P and Zannad F. Cohort Profile: Rationale and design of the fourth visit of the STANISLAS cohort: a familial longitudinal population-based cohort from the Nancy region of France. *Int J Epidemiol*. 2018;47:395-395j.

10. Ferreira JP, Girerd N, Bozec E, Mercklé L, Pizard A, Bouali S, Eby E, Leroy C, Machu J-L, Boivin J-M, Lamiral Z, Rossignol P and Zannad F. Cohort Profile: Rationale and design of the fourth visit of the STANISLAS cohort: a familial longitudinal population-based cohort from the Nancy region of France. *International Journal of Epidemiology*. 2017;47:395-395j.

11. Schwartz GJ, Haycock GB, Edelmann CM, Jr. and Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. *Pediatrics*. 1976;58:259-63.

12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T and Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-12.

13. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation*. 2002;106:3143-3143.

14. Cole TJ and Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes*. 2012;7:284-94.

15. Sharma AK, Metzger DL, Daymont C, Hadjiyannakis S and Rodd CJ. LMS tables for waist-circumference and waist-height ratio Z-scores in children aged 5-19 y in NHANES III: association with cardio-metabolic risks. *Pediatr Res*. 2015;78:723-9.

16. Cole TJ, Bellizzi MC, Flegal KM and Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ (Clinical research ed)*. 2000;320:1240-3.

17. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H and European Network for Non-invasive Investigation of Large A. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006;27:2588-605.
18. Goncalves N, Gomes-Ferreira C, Moura C, Roncon-Albuquerque R, Jr., Leite-Moreira AF and Falcao-Pires I. Worse cardiac remodeling in response to pressure overload in type 2 diabetes mellitus. *Int J Cardiol*. 2016;217:195-204.
19. Tzemos N, Lyseggen E, Silversides C, Jamorski M, Tong JH, Harvey P, Floras J and Siu S. Endothelial function, carotid-femoral stiffness, and plasma matrix metalloproteinase-2 in men with bicuspid aortic valve and dilated aorta. *J Am Coll Cardiol*. 2010;55:660-8.
20. Peeters SA, Engelen L, Buijs J, Chaturvedi N, Fuller JH, Jorsal A, Parving HH, Tarnow L, Theilade S, Rossing P, Schalkwijk CG and Stehouwer CDA. Circulating matrix metalloproteinases are associated with arterial stiffness in patients with type 1 diabetes: pooled analysis of three cohort studies. *Cardiovascular diabetology*. 2017;16:139.
21. Yasmin, McEniery CM, Wallace S, Dakham Z, Pulsalkar P, Maki-Petaja K, Ashby MJ, Cockcroft JR and Wilkinson IB. Matrix metalloproteinase-9 (MMP-9), MMP-2, and serum elastase activity are associated with systolic hypertension and arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2005;25:372.
22. Skrypnik D, Mostowska A, Jagodziński PP and Bogdański P. Association of rs699947 (-2578 C/A) and rs2010963 (-634 G/C) Single Nucleotide Polymorphisms of the VEGF Gene, VEGF-A and Leptin Serum Level, and Cardiovascular Risk in Patients with Excess Body Mass: A Case–Control Study. *Journal of Clinical Medicine*. 2020;9:469.
23. Hassanisaber H, Rouleau L and Fauchoux N. Effect of BMP-9 on endothelial cells and its role in atherosclerosis. *Frontiers in bioscience (Landmark edition)*. 2019;24:994-1023.
24. Wang J, Razuvaev A, Folkersen L, Hedin E, Roy J, Brismar K and Hedin U. The

expression of IGFs and IGF binding proteins in human carotid atherosclerosis, and the possible role of IGF binding protein-1 in the regulation of smooth muscle cell proliferation.

Atherosclerosis. 2012;220:102-9.

25. Bazzichi L, Ghiadoni L, Rossi A, Bernardini M, Lanza M, De Feo F, Giacomelli C, Mencaroni I, Raimo K, Rossi M, Mazzone AM, Taddei S and Bombardieri S. Osteopontin is associated with increased arterial stiffness in rheumatoid arthritis. *Molecular medicine (Cambridge, Mass)*. 2009;15:402-6.

26. Bui AL, Katz R, Kestenbaum B, de Boer IH, Fried LF, Polak JF, Wasserman BA, Sarnak MJ, Siscovick D and Shlipak MG. Cystatin C and carotid intima-media thickness in asymptomatic adults: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis*. 2009;53:389-98.

27. Aleksandrova K, Mozaffarian D and Pischon T. Addressing the Perfect Storm: Biomarkers in Obesity and Pathophysiology of Cardiometabolic Risk. *Clinical chemistry*. 2018;64:142-153.

28. Bayes-Genis A, Cediël G, Domingo M, Codina P, Santiago E and Lupón J. Biomarkers in Heart Failure with Preserved Ejection Fraction. *Cardiac failure review*. 2022;8:e20.

29. Nimptsch K, Konigorski S and Pischon T. Diagnosis of obesity and use of obesity biomarkers in science and clinical medicine. *Metabolism: clinical and experimental*. 2019;92:61-70.

30. Enroth S, Maturi V, Berggrund M, Enroth SB, Moustakas A, Johansson A and Gyllenstein U. Systemic and specific effects of antihypertensive and lipid-lowering medication on plasma protein biomarkers for cardiovascular diseases. *Sci Rep*. 2018;8:5531.

31. Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, Simonovic M, Doncheva NT, Morris JH, Bork P, Jensen LJ and Mering CV. STRING v11: protein-protein

association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. *Nucleic acids research*. 2019;47:D607-d613.

32. Fabregat A, Korninger F, Viteri G, Sidiropoulos K, Marin-Garcia P, Ping P, Wu G, Stein L, D'Eustachio P and Hermjakob H. Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*. 2018;14:e1005968.

33. Grundy SM, Brewer HB, Cleeman JI, Smith SC and Lenfant C. Definition of Metabolic Syndrome. *Circulation*. 2004;109:433-438.

34. Charakida M, Jones A, Falaschetti E, Khan T, Finer N, Sattar N, Hingorani A, Lawlor DA, Smith GD and Deanfield JE. Childhood obesity and vascular phenotypes: a population study. *J Am Coll Cardiol*. 2012;60:2643-50.

35. Aatola H, Hutri-Kähönen N, Juonala M, Laitinen TT, Pahkala K, Mikkilä V, Telama R, Koivisto T, Lehtimäki T, Viikari JS, Raitakari OT and Kähönen M. Prospective relationship of change in ideal cardiovascular health status and arterial stiffness: the Cardiovascular Risk in Young Finns Study. *J Am Heart Assoc*. 2014;3:e000532.

36. Buscot MJ, Thomson RJ, Juonala M, Sabin MA, Burgner DP, Lehtimäki T, Hutri-Kähönen N, Viikari JSA, Raitakari OT and Magnussen CG. Distinct child-to-adult body mass index trajectories are associated with different levels of adult cardiometabolic risk. *Eur Heart J*. 2018;39:2263-2270.

37. Charakida M, Khan T, Johnson W, Finer N, Woodside J, Whincup PH, Sattar N, Kuh D, Hardy R and Deanfield J. Lifelong patterns of BMI and cardiovascular phenotype in individuals aged 60-64 years in the 1946 British birth cohort study: an epidemiological study. *The lancet Diabetes & endocrinology*. 2014;2:648-54.

38. de Divitiis O, Fazio S, Petitto M, Maddalena G, Contaldo F and Mancini M. Obesity and cardiac function. *Circulation*. 1981;64:477-82.

39. Kasper EK, Hruban RH and Baughman KL. Cardiomyopathy of obesity: a

clinicopathologic evaluation of 43 obese patients with heart failure. *The American journal of cardiology*. 1992;70:921-4.

40. Smulyan H, Marchais SJ, Pannier B, Guerin AP, Safar ME and London GM. Influence of body height on pulsatile arterial hemodynamic data. *Journal of the American College of Cardiology*. 1998;31:1103-9.

41. Zore T, Palafox M and Reue K. Sex differences in obesity, lipid metabolism, and inflammation-A role for the sex chromosomes? *Molecular metabolism*. 2018;15:35-44.

42. Goossens GH, Jocken JWE and Blaak EE. Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver. *Nature reviews Endocrinology*. 2021;17:47-66.

43. Davis PH, Dawson JD, Riley WA and Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. *Circulation*. 2001;104:2815-9.

44. Chau K, Girerd N, Bozec E, Ferreira JP, Duarte K, Nazare JA, Laville M, Benetos A, Zannad F, Boivin JM and Rossignol P. Association between abdominal adiposity and 20-year subsequent aortic stiffness in an initially healthy population-based cohort. *J Hypertens*. 2018;36:2077-2084.

45. Lischka J, Schanzer A, Hojreh A, Ba-Ssalamah A, de Gier C, Valent I, Item CB, Greber-Platzer S and Zeyda M. Circulating microRNAs 34a, 122, and 192 are linked to obesity-associated inflammation and metabolic disease in pediatric patients. *International journal of obesity (2005)*. 2021;45:1763-1772.

46. Ferrante AW, Jr. Obesity-induced inflammation: a metabolic dialogue in the language of inflammation. *Journal of internal medicine*. 2007;262:408-14.

47. Ridker PM and Rane M. Interleukin-6 Signaling and Anti-Interleukin-6 Therapeutics in Cardiovascular Disease. *Circulation research*. 2021;128:1728-1746.

48. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*. 2011;117:3720-32.
49. Dinarello CA, Simon A and van der Meer JW. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. *Nature reviews Drug discovery*. 2012;11:633-52.
50. Amar J, Fauvel J, Drouet L, Ruidavets JB, Perret B, Chamontin B, Boccalon H and Ferrieres J. Interleukin 6 is associated with subclinical atherosclerosis: a link with soluble intercellular adhesion molecule 1. *J Hypertens*. 2006;24:1083-8.
51. Lee WY, Allison MA, Kim DJ, Song CH and Barrett-Connor E. Association of interleukin-6 and C-reactive protein with subclinical carotid atherosclerosis (the Rancho Bernardo Study). *The American journal of cardiology*. 2007;99:99-102.
52. Wolters TLC, Netea MG, Hermus A, Smit JWA and Netea-Maier RT. IGF1 potentiates the pro-inflammatory response in human peripheral blood mononuclear cells via MAPK. *Journal of molecular endocrinology*. 2017;59:129-139.
53. Maffei P, Dassie F, Wennberg A, Parolin M and Vettor R. The Endothelium in Acromegaly. *Frontiers in endocrinology*. 2019;10:437.
54. Budatha M, Zhang J and Schwartz MA. Fibronectin-Mediated Inflammatory Signaling Through Integrin $\alpha 5$ in Vascular Remodeling. *Journal of the American Heart Association*. 2021;10:e021160.
55. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR and Clegg LX. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *American journal of epidemiology*. 1997;146:483-94.
56. Salonen JT and Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arteriosclerosis and thrombosis : a journal of vascular*

biology. 1991;11:1245-9.

57. Powell-Wiley TM, Poirier P, Burke LE, Després JP, Gordon-Larsen P, Lavie CJ, Lear SA, Ndumele CE, Neeland IJ, Sanders P and St-Onge MP. Obesity and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 2021;143:e984-e1010.

58. Hettwer J, Hinterdobler J, Miritsch B, Deutsch MA, Li X, Mauersberger C, Moggio A, Braster Q, Gram H, Robertson AAB, Cooper MA, Groß O, Krane M, Weber C, Koenig W, Soehnlein O, Adamstein NH, Ridker P, Schunkert H, Libby P, Kessler T and Sager HB. Interleukin-1 β suppression dampens inflammatory leukocyte production and uptake in atherosclerosis. *Cardiovascular research*. 2021.

59. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P and Glynn RJ. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *The New England journal of medicine*. 2017;377:1119-1131.

Graphical abstract

BMI, body mass index; IMT, intima media thickness; MMP3, matrix metalloproteinase-3; OPN, osteopontin; IGFBP1; insulin-like growth factor-1; IGFBP2, insulin-like growth factor-2; IFNG, interferon-gamma; LEP, leptin; FABP4, fatty acid-binding protein-4; CRP, C-reactive protein; VEGF-A, vascular endothelial growth factor-A; IL-6, interleukin-6; IGF-1, insulin-like growth factor-1; FN, fibronectin.

Figure 1. Univariable model for the association of childhood-to-adult adiposity with adult cIMT

Abbreviations are presented in Table 1.

Figure 2. Network analysis relating the top proteins associated with body mass index and/or waist-height-ratio in children

Network analysis presents that the top proteins are associated with higher vs lower levels of body mass index and/or waist-height-ratio in children.

MMP3, matrix metalloproteinase-3; OPN, osteopontin; IGFBP-1; insulin-like growth factor-1; IGFBP-2, insulin-like growth factor-2; IFNG, interferon-gamma; LEP, leptin; FABP-4, fatty acid-binding protein-4; CRP, C-reactive protein; VEGF-A, vascular endothelial growth factor-A; IL-6, interleukin-6; IGF-1, insulin-like growth factor-1; FN, fibronectin.

Graphical abstract

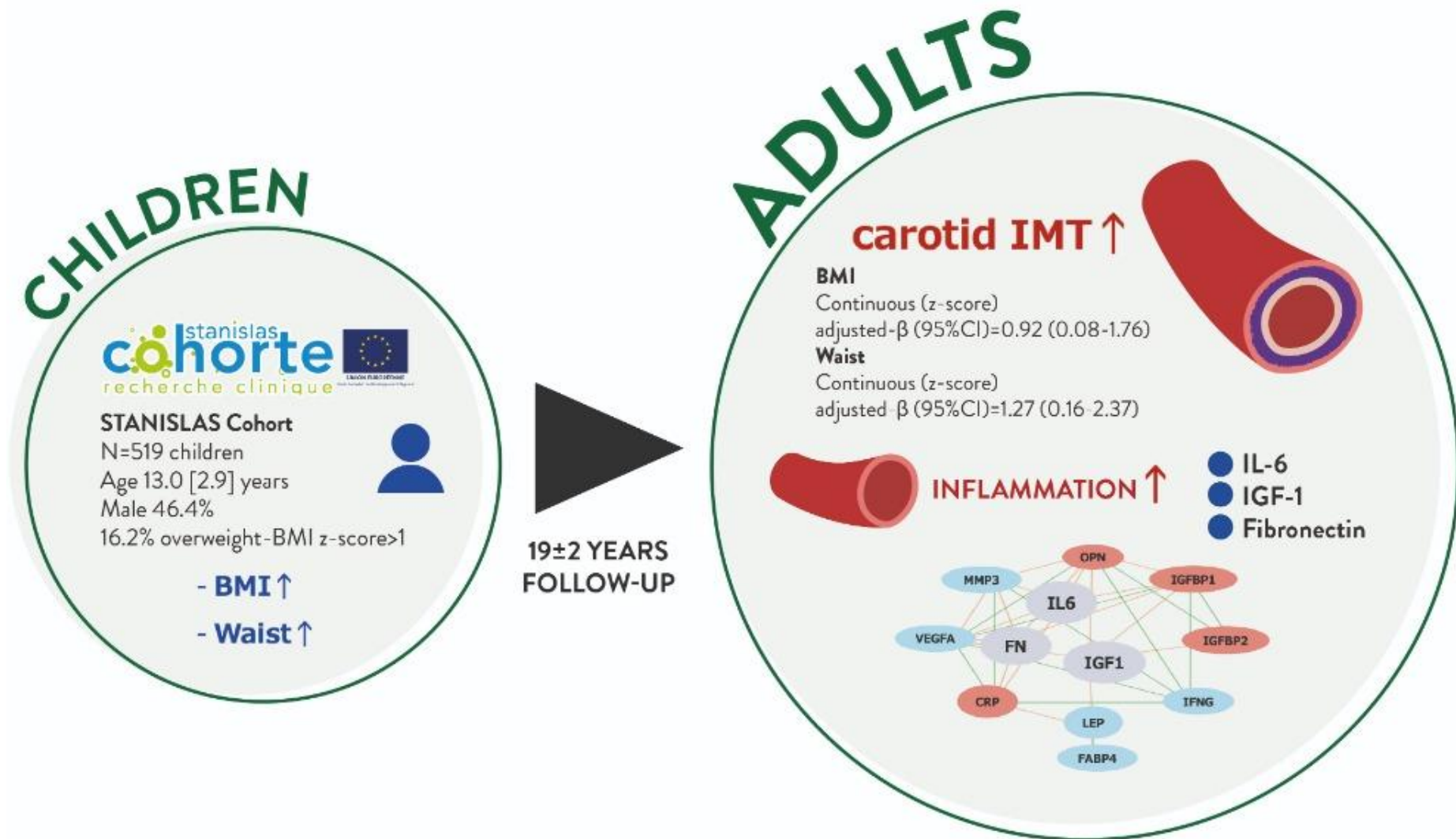


Figure 1. Univariable model for the association of childhood-to-adult adiposity with adult cIMT

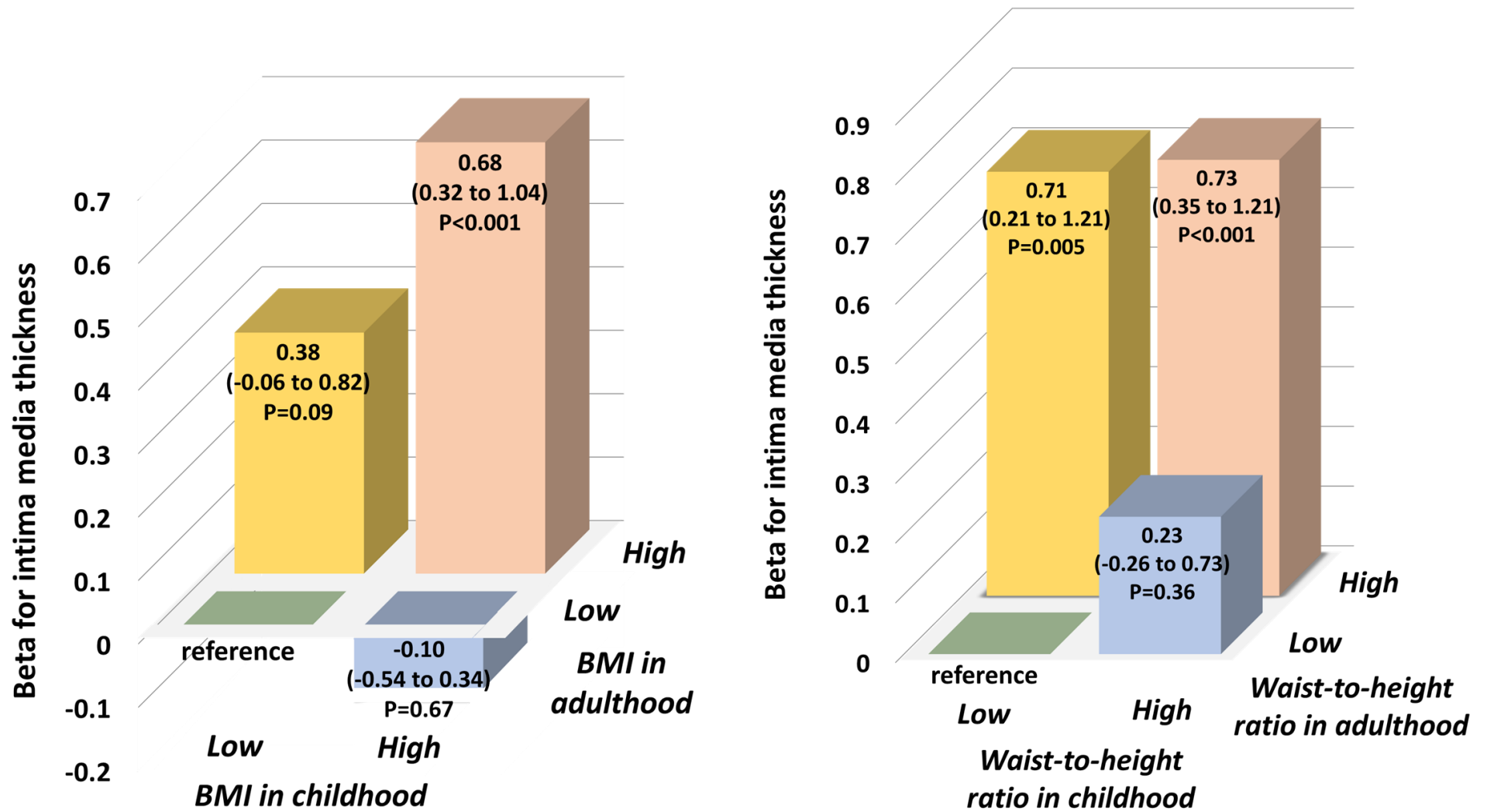


Figure 2. Network analysis relating the top proteins associated with body mass index and/or waist-height-ratio in children

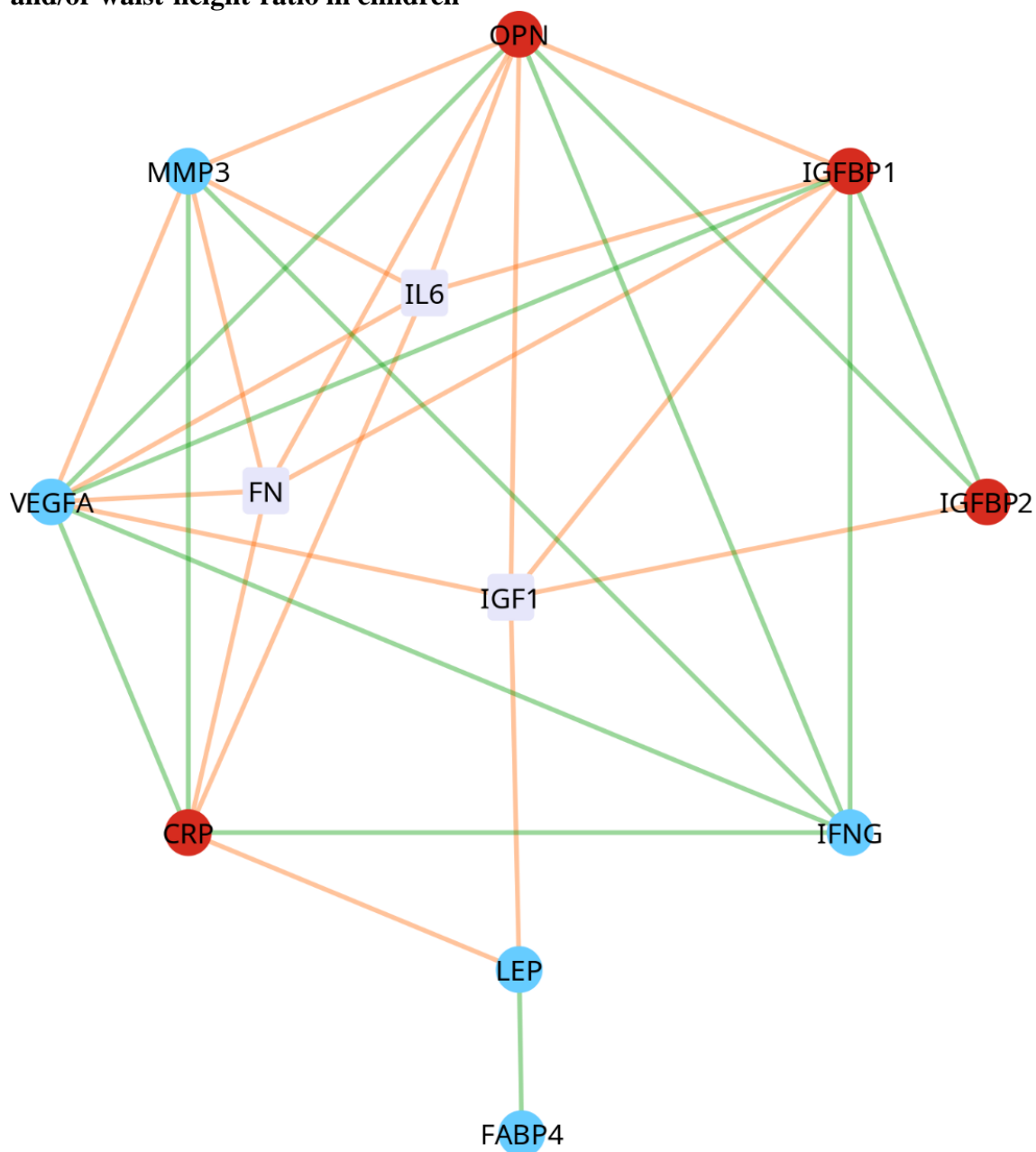


Table 1. Baseline characteristics according to the tertiles of BMI and waist-to-height ratio z-scores in children

Values are expressed as mean \pm SD, n (%) or median (25th to 75th percentile)

BMI was converted to age- and sex-specific z score based on the International Obesity Task Force (IOTF)¹, while waist-to-height ratio was based on the Third National Health and Nutrition Examination Survey².

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate, CRP, C-reactive protein; MET, metabolic equivalent; IMT, intima media thickness.

Table 2. Linear regression analyses of the association between childhood adiposity and adult cIMT

A dependent variable was 10 μ m increase in adult carotid intima media thickness.

BMI was converted to age- and sex-specific z score based on the International Obesity Task Force (IOTF)¹, while waist-to-height ratio and waist circumference were based on the Third National Health and Nutrition Examination Survey². Overweight and obesity were respectively defined by a BMI z-score >1 and >2 as proposed by the IOTF³.

Model for the childhood period included age, sex, systolic blood pressure, blood glucose, total cholesterol, and triglycerides. Model for the adult period included age, sex, metabolic syndrome, hypertension, systolic blood pressure, blood glucose, total cholesterol, and triglycerides.

CI, confidential interval; remaining abbreviations are presented in Table 1.

(References)

1. Cole TJ and Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes.* 2012;7:284-94.
2. Sharma AK, Metzger DL, Daymont C, Hadjiyannakis S and Rodd CJ. LMS tables for waist-circumference and waist-height ratio Z-scores in children aged 5-19 y in NHANES III: association with cardio-metabolic risks. *Pediatr Res.* 2015;78:723-9.
3. Cole TJ, Bellizzi MC, Flegal KM and Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ (Clinical research ed).* 2000;320:1240-3.

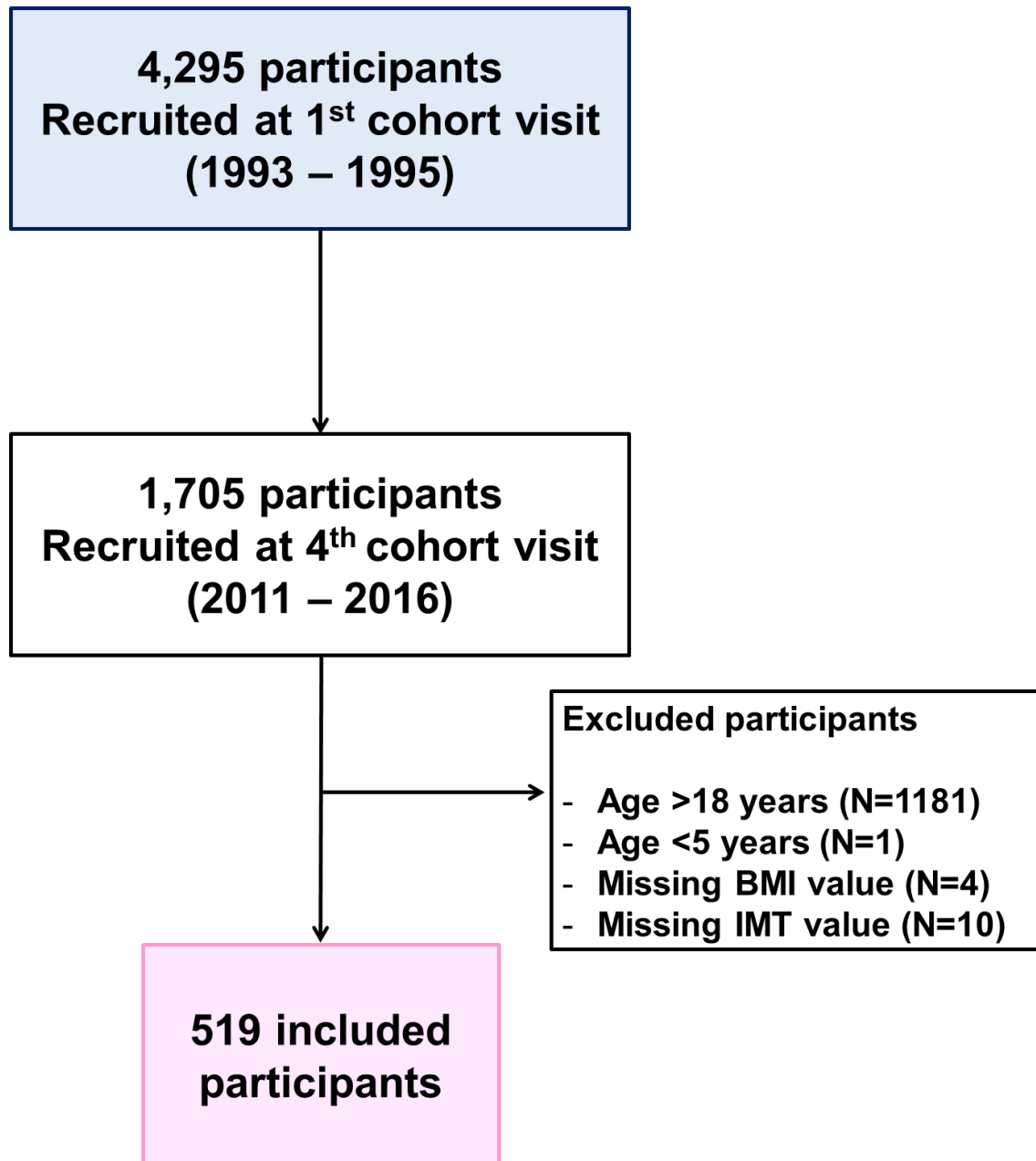
Table 1. Baseline characteristics according to the tertiles of BMI and waist-to-height ratio z-scores in children

	BMI z score tertile			p-value	Waist-to-height ratio z score tertile			p-value
	T1, < -0.35 (N=173)	T2, -0.35 - 0.40 (N=173)	T3, > 0.40 (N=173)		T1, < -1.20 (N=148)	T2, -1.20 - -0.53 (N=146)	T3, > -0.53 (N=146)	
Variables for the childhood period								
Age, years	12.5 ± 2.9	12.9 ± 2.9	13.1 ± 2.8	0.13	13.0 ± 2.8	12.9 ± 2.9	13.1 ± 2.8	0.84
Age ≥14 years, N (%)	57 (32.9 %)	73 (42.2 %)	71 (41.0 %)	0.16	56 (37.6 %)	66 (44.0 %)	58 (39.2 %)	0.50
Male, N (%)	83 (48.0 %)	81 (46.8 %)	77 (44.5 %)	0.81	35 (23.5 %)	73 (48.7 %)	98 (66.2 %)	<0.001
Height, cm	150 ± 16	154 ± 16	157 ± 15	<0.001	155 ± 14	154 ± 17	154 ± 15	0.83
Weight, kg	37 ± 11	44 ± 12	54 ± 15	<0.001	41 ± 11	44 ± 13	51 ± 16	<0.001
BMI (z score)	-0.91 ± 0.48	-0.02 ± 0.21	1.05 ± 0.49	<0.001	-0.63 ± 0.68	-0.01 ± 0.62	0.79 ± 0.79	<0.001
Waist circumference, cm	59 ± 6	63 ± 6	69 ± 8	<0.001	59 ± 5	63 ± 6	69 ± 8	<0.001
Waist/Height ratio	0.39 ± 0.02	0.41 ± 0.02	0.44 ± 0.03	<0.001	0.38 ± 0.01	0.41 ± 0.01	0.45 ± 0.03	<0.001
Regular sports activity	105 (60.7 %)	108 (62.4 %)	113 (65.3 %)	0.67	89 (59.7 %)	95 (63.3 %)	103 (69.6 %)	0.20
Means for commuting to school								
Walking	73 (42.2 %)	64 (37.0 %)	62 (35.8 %)	0.55	62 (41.6 %)	64 (42.7 %)	48 (32.4 %)	0.19
Bicycle	3 (1.7 %)	3 (1.7 %)	1 (0.6 %)		4 (2.7 %)	1 (0.7 %)	2 (1.4 %)	
Other	97 (56.1 %)	106 (61.3 %)	110 (63.6 %)		83 (55.7 %)	85 (56.7 %)	98 (66.2 %)	
Birth weight, g	3231 ± 481	3265 ± 452	3376 ± 414	0.06	3235 ± 394	3314 ± 484	3309 ± 518	0.44
Birth height, cm	55 ± 45	50 ± 2	50 ± 2	0.33	50 ± 2	50 ± 2	50 ± 2	0.37
Systolic BP, mmHg	118 ± 11	119 ± 10	120 ± 13	0.55	117 ± 9	119 ± 12	121 ± 12	0.03
Diastolic BP, mmHg	62 ± 11	65 ± 10	65 ± 10	0.053	64 ± 10	62 ± 12	66 ± 9	0.02
Heart rate, bpm	72 ± 12	70 ± 11	68 ± 11	0.08	72 ± 11	70 ± 12	68 ± 11	0.04
Total cholesterol, g/l	1.84 ± 0.30	1.80 ± 0.30	1.84 ± 0.32	0.38	1.83 ± 0.31	1.81 ± 0.31	1.84 ± 0.32	0.57
Triglyceride, g/l	0.65 ± 0.35	0.64 ± 0.29	0.68 ± 0.33	0.35	0.64 ± 0.28	0.66 ± 0.36	0.68 ± 0.32	0.55
eGFR, ml/min/1.73m ²	126 ± 20	126 ± 21	126 ± 19	0.95	123 ± 19	128 ± 18	129 ± 23	0.02
CRP, mg/l	0.17 (0.16 - 0.43)	0.22 (0.16 - 0.52)	0.45 (0.21 - 0.95)	<0.001	0.17 (0.16 - 0.53)	0.27 (0.16 - 0.45)	0.38 (0.17 - 0.81)	<0.001
Variables for the adult period								
Age, yrs	31.3 ± 3.8	31.3 ± 4.1	31.9 ± 3.7	0.20	31.6 ± 3.7	31.6 ± 3.5	31.9 ± 3.7	0.66
Height, cm	171 ± 9	171 ± 9	171 ± 10	0.97	170 ± 8	171 ± 9	173 ± 9	0.018
BMI, kg/m ²	22 ± 3	24 ± 3	27 ± 5	<0.001	22 ± 3	24 ± 4	27 ± 5	<0.001
Hypertension, N (%)	3 (1.7 %)	4 (2.3 %)	7 (4.0 %)	0.39	4 (2.7 %)	3 (2.0 %)	5 (3.4 %)	0.76
Diabetes mellitus, N (%)	1 (0.6 %)	1 (0.6 %)	2 (1.2 %)	0.78	2 (1.3 %)	0 (0.0 %)	1 (0.7 %)	0.36
Metabolic syndrome, N (%)	2 (1.2 %)	3 (1.7 %)	13 (7.5 %)	0.002	1 (0.7 %)	4 (2.7 %)	11 (7.4 %)	0.006
Total MET, MET/min/week	1578 (552 - 3930)	1288 (356 - 2816)	1580 (690 - 4044)	0.10	1212 (445 - 2945)	1438 (507 - 2868)	1427 (594 - 4158)	0.33
Systolic BP, mmHg	114 ± 13	114 ± 13	115 ± 14	0.65	110 ± 12	114 ± 13	117 ± 14	<0.001
Diastolic BP, mmHg	65 ± 8	65 ± 7	66 ± 9	0.19	64 ± 7	65 ± 8	67 ± 9	<0.001
Heart rate, bpm	66 ± 9	63 ± 9	63 ± 9	0.004	65 ± 8	63 ± 10	63 ± 9	0.06
Total cholesterol, g/l	1.94 ± 0.36	1.96 ± 0.34	1.93 ± 0.33	0.78	1.96 ± 0.32	1.91 ± 0.38	1.97 ± 0.32	0.30
Triglyceride, g/l	0.92 ± 0.59	0.91 ± 0.50	0.97 ± 0.52	0.61	0.90 ± 0.47	0.93 ± 0.63	1.01 ± 0.56	0.22
Carotid IMT, μm	517 (468 - 563)	522 (484 - 579)	528 (475 - 598)	0.15	518 (475 - 572)	514 (478 - 562)	540 (478 - 610)	0.038

Table 2. Linear regression analyses of the association between childhood adiposity and adult cIMT

	Models with covariates measured in the childhood period						Models with covariates measured at the adult period	
	Crude model		without CRP		with CRP		adjusted-beta (95%CI)	p
	beta (95% CI)	p	adjusted-beta (95%CI)	p	adjusted-beta (95%CI)	p		
Body mass index								
Continuous	0.55 (0.31 to 0.78)	<0.001	0.36 (0.01 to 0.72)	0.043	0.28 (-0.09 to 0.65)	0.14	0.44 (0.16 to 0.73)	0.002
Continuous (z-score)	0.97 (0.16 to 1.79)	0.02	0.91 (-0.06 to 1.89)	0.07	0.74 (-0.27 to 1.74)	0.15	0.92 (0.08 to 1.76)	0.03
Tertile, T1	(reference)		(reference)		(reference)		(reference)	
T2	1.35 (-0.46 to 0.05)	0.14	1.67 (-0.50 to 3.85)	0.13	1.96 (-0.20 to 4.11)	0.08	1.48 (-0.40 to 3.35)	0.12
T3	1.86 (3.16 to 3.67)	0.04	1.67 (-0.52 to 3.85)	0.13	1.40 (-0.80 to 3.59)	0.21	1.69 (-0.18 to 3.56)	0.08
Overweight	1.52 (-0.50 to 3.53)	0.14	1.91 (-0.54 to 4.35)	0.17	0.82 (-1.79 to 3.44)	0.54	1.69 (-0.38 to 3.76)	0.11
Obesity	6.47 (0.11 to 12.82)	0.046	4.74 (-2.37 to 11.85)	0.19	1.80 (-5.77 to 9.37)	0.64	4.18 (-1.99 to 10.35)	0.18
Waist/Height								
Continuous	2.39 (-0.02 to 4.80)	0.052	2.09 (-0.95 to 5.13)	0.18	1.16 (-2.03 to 4.36)	0.47	1.53 (-1.05 to 4.10)	0.24
Continuous (z-score)	1.41 (0.36 to 2.46)	0.009	0.78 (-0.57 to 2.13)	0.26	0.36 (-1.03 to 1.75)	0.61	0.69 (-0.47 to 1.86)	0.24
Tertile, T1	(reference)		(reference)		(reference)		(reference)	
T2	0.05 (-1.93 to 2.02)	0.96	-0.57 (-2.90 to 1.76)	0.63	-0.41 (-2.74 to 1.91)	0.73	-0.96 (-2.98 to 1.06)	0.35
T3	2.77 (0.79 to 4.74)	0.006	0.86 (-1.64 to 3.37)	0.50	0.69 (-1.88 to 3.26)	0.60	0.97 (-1.17 to 3.12)	0.37
Waist circumference								
Continuous	0.31 (0.21 to 0.41)	<0.001	0.20 (0.03 to 0.37)	0.02	0.14 (-0.03 to 0.31)	0.11	0.22 (0.09 to 0.36)	0.001
Continuous (z-score)	1.76 (0.75 to 2.77)	0.001	1.40 (0.15 to 2.65)	0.03	1.02 (-0.25 to 2.29)	0.12	1.27 (0.16 to 2.37)	0.03
Tertile, T1	(reference)		(reference)		(reference)		(reference)	
T2	1.52 (-0.45 to 3.50)	0.13	1.37 (-0.94 to 3.68)	0.24	1.69 (-0.61 to 3.98)	0.15	0.05 (-1.98 to 2.07)	0.96
T3	2.89 (0.91 to 4.87)	0.004	1.69 (-0.74 to 4.11)	0.17	0.78 (-1.65 to 3.20)	0.53	1.28 (-0.83 to 3.40)	0.23

Supplemental Figure 1. Study flow chart



Supplemental Table 1. Baseline characteristics according to the tertiles of waist circumference z-score

	Waist circumference z-score tertile			p-value
	T1, -4.60 - -0.99 (N=147)	T2, -0.99 - -0.32 (N=148)	T3, -0.32 - 1.79 (N=145)	
Variables for the childhood period				
Age, years	12.7 ± 2.8	13.1 ± 2.9	13.1 ± 2.8	0.40
Age ≥ 14 years, N (%)	53 (35.1 %)	63 (42.9 %)	64 (43.0 %)	0.28
Male, N (%)	42 (27.8 %)	73 (49.7 %)	91 (61.1 %)	<0.001
Height, cm	149 ± 14	155 ± 15	159 ± 15	<0.001
Weight, kg	38 ± 10	45 ± 12	54 ± 15	<0.001
BMI (z score)	-0.66 ± 0.65	-0.05 ± 0.64	0.86 ± 0.69	<0.001
Waist circumference, cm	58 ± 4	64 ± 5	71 ± 7	<0.001
Waist/Height ratio	0.39 ± 0.02	0.41 ± 0.02	0.44 ± 0.03	<0.001
Regular sports activity	89 (58.9 %)	101 (68.7 %)	97 (65.1 %)	0.20
Means of commuting to school				
Walking	61 (40.4 %)	59 (40.1 %)	54 (36.2 %)	0.31
Bicycle	4 (2.6 %)	3 (2.0 %)	0 (0.0 %)	
Other	86 (57.0 %)	85 (57.8 %)	95 (63.8 %)	
Commuting time (min/week)	100 (60 - 200)	120 (90 - 250)	130 (80 - 210)	0.57
Birth weight, g	3185 ± 448	3288 ± 429	3387 ± 506	0.015
Birth height, cm	50 ± 2	50 ± 2	50 ± 2	0.60
Systolic BP, mmHg	116 ± 10	119 ± 10	122 ± 13	0.003
Diastolic BP, mmHg	61 ± 11	64 ± 11	67 ± 9	<0.001
Heart rate, bpm	72 ± 12	71 ± 10	67 ± 11	0.003
Total cholesterol, g/l	1.86 ± 0.30	1.83 ± 0.32	1.79 ± 0.31	0.18
Triglyceride, g/l	0.65 ± 0.26	0.65 ± 0.35	0.68 ± 0.34	0.66
eGFR, ml/min/1.73m ²	121 ± 18	127 ± 21	131 ± 20	<0.001
CRP, mg/l	0.17 (0.16 - 0.53)	0.26 (0.16 - 0.54)	0.35 (0.17 - 0.76)	0.001
Variables for the adult period				
Age, yrs	31.4 ± 3.7	32.0 ± 3.4	31.8 ± 3.9	0.36
Height, cm	167 ± 8	172 ± 8	175 ± 9	<0.001
Body mass index, kg/m ²	22 ± 3	24 ± 4	27 ± 5	<0.001
Hypertension	3 (2.0 %)	4 (2.7 %)	5 (3.4 %)	0.76
Diabetes	2 (1.3 %)	0 (0.0 %)	1 (0.7 %)	0.38
Metabolic syndrome	0 (0.0 %)	5 (3.4 %)	11 (7.4 %)	0.003
Total MET, MET/min/week	1188 (432 - 3012)	1326 (463 - 2775)	1488 (720 - 4044)	0.14
Systolic BP, mmHg	110 ± 11	114 ± 14	117 ± 13	<0.001
Diastolic BP, mmHg	63 ± 7	66 ± 8	67 ± 9	<0.001
Heart rate, bpm	66 ± 8	63 ± 8	62 ± 9	<0.001
Total cholesterol, g/l	1.93 ± 0.32	1.97 ± 0.38	1.94 ± 0.32	0.55
Triglyceride, g/l	0.89 ± 0.47	0.90 ± 0.55	1.05 ± 0.63	0.018
Carotid IMT, μm	518 (466 - 561)	526 (486 - 586)	532 (477 - 602)	0.08

Values are expressed as mean ±SD, n (%) or median (25th to 75th percentile)

Waist circumference was converted to age- and sex-specific z score based on the Third National Health and Nutrition Examination Survey ¹.

BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate, CRP, C-reactive protein; MET, metabolic equivalent; IMT, intima media thickness.

(reference)

1.Sharma AK, Metzger DL, Daymont C, Hadjiyannakis S and Rodd CJ. LMS tables for waist-circumference and waist-height ratio Z-scores in children aged 5-19 y in NHANES III: association with cardio-metabolic risks. *Pediatr Res.* 2015;78:723-9.

Supplemental Table 2. Linear regression analyses for the association between childhood adiposity and adult IMT according to men and women

	Women			Men			p-value for interaction with sex difference
	beta (95% CI)		p-value	beta (95% CI)		p-value	
Body mass index							
Continuous (z-score)	0.94	-0.03 to 1.90	0.06	1.08	-0.25 to 2.42	0.11	0.86
Tertile, T1		(reference)			(reference)		0.004
T2	2.05	-0.07 to 4.16	0.06	0.64	-2.33 to 3.60	0.67	
T3	2.03	-0.07 to 4.13	0.06	1.90	-1.10 to 4.89	0.21	
Overweight	0.98	-1.36 to 3.32	0.41	2.28	-1.06 to 5.62	0.18	0.52
Obesity	8.45	0.17 to 16.74	0.046	4.37	-5.06 to 13.8	0.36	0.53
Waist/Height							
Continuous (z-score)	1.15	-0.21 to 2.51	0.10	0.34	-1.41 to 2.08	0.71	0.46
Tertile, T1		(reference)			(reference)		0.003
T2	-0.12	-2.30 to 2.06	0.92	-2.40	-6.33 to 1.54	0.23	
T3	2.05	-0.46 to 4.55	0.11	-0.11	-3.88 to 3.66	0.95	
Waist circumference							
Continuous (z-score)	1.73	0.46 to 2.99	0.008	0.80	-0.85 to 2.46	0.34	0.38
Tertile, T1		(reference)			(reference)		0.002
T2	2.14	-0.08 to 4.35	0.06	-1.47	-5.21 to 2.27	0.44	
T3	1.93	-0.47 to 4.32	0.11	0.67	-3.00 to 4.31	0.72	

BMI was converted to age- and sex-specific z score based on the International Obesity Task Force (IOTF), while waist-to-height ratio and waist circumference were based on the Third National Health and Nutrition Examination Survey. Overweight and obesity were respectively defined by a BMI z-score >1 and >2 as proposed by the IOTF.

Supplemental Table 3. Associations between childhood-to-adult adiposity and adult IMT in multivariable models

	Univariable			Multivariable		
	beta	95%CI	p-value	beta	95%CI	p-value
Body mass index						
Low in children & Low in adults		(reference)			(reference)	
High in children & Low in adults	-0.10	-0.54 to 0.34	0.67	0.18	-0.43 to 0.80	0.56
Low in children & High in adults	0.38	-0.06 to 0.82	0.092	0.21	-0.37 to 0.79	0.48
High in children & High in adults	0.68	0.32 to 1.04	<0.001	0.63	0.12 to 1.14	0.015
Waist/Height ratio						
Low in children & Low in adults		(reference)			(reference)	
High in children & Low in adults	0.23	-0.26 to 0.73	0.36	0.46	-0.17 to 1.08	0.15
Low in children & High in adults	0.71	0.21 to 1.21	0.005	0.70	0.06 to 1.34	0.033
High in children & High in adults	0.73	0.35 to 1.12	<0.001	0.48	-0.05 to 1.01	0.074
Waist circumference						
Low in children & Low in adults		(reference)			(reference)	
High in children & Low in adults	0.35	-0.15 to 0.86	0.17	0.46	-0.21 to 1.13	0.18
Low in children & High in adults	0.47	-0.01 to 0.95	0.055	0.12	-0.56 to 0.80	0.73
High in children & High in adults	0.85	0.46 to 1.24	<0.001	0.38	-0.21 to 0.97	0.20

The multivariable model included variables measured in the childhood period (i.e., birth weight, systolic BP, heart rate, total cholesterol, eGFR, natural log of C-reactive protein) and those measured in the adult period (i.e., height, metabolic syndrome, peripheral systolic BP and heart rate).

Supplemental Table 4. Circulating proteins associated with body mass index and waist-to-height ratio z-scores

	BMI z-scores >T3 vs <T1			Waist/Height z-scores >T3 vs <T1		
	Adjusted-OR (95%CI)	p-value	FDR	Adjusted-OR (95%CI)	p-value	FDR
IGFBP-1	1.43 (1.14 - 1.80)	0.002	0.011	1.29 (1.01 - 1.63)	0.11	0.19
IGFBP-2	1.86 (1.37 - 2.52)	<0.001	<0.001	2.58 (1.82 - 3.66)	<0.001	<0.001
MMP-2	2.03 (1.09 - 3.79)	0.057	0.16	1.03 (0.48 - 2.21)	0.99	0.99
MMP-3	0.79 (0.55 - 1.15)	0.12	0.22	1.91 (1.30 - 2.80)	0.003	0.009
MMP-9	0.87 (0.64 - 1.19)	0.66	0.70	1.21 (0.89 - 1.66)	0.32	0.44
Osteopontin	1.38 (0.89 - 2.12)	0.011	0.04	3.09 (1.80 - 5.29)	<0.001	<0.001
VEGF-A	0.40 (0.26 - 0.61)	<0.001	<0.001	1.25 (0.82 - 1.91)	0.034	0.071
BMP-9	0.77 (0.52 - 1.14)	0.42	0.50	0.53 (0.32 - 0.89)	0.021	0.05
FABP-4	1.25 (0.81 - 1.93)	0.60	0.67	0.42 (0.27 - 0.65)	<0.001	<0.001
Leptin	0.64 (0.40 - 1.02)	0.16	0.28	0.43 (0.34 - 0.54)	<0.001	<0.001
Resistin	0.82 (0.66 - 1.03)	0.20	0.31	1.70 (1.00 - 2.89)	0.12	0.19
Cystatin-C	1.25 (0.81 - 1.93)	0.091	0.20	1.51 (0.89 - 2.58)	0.14	0.21
KIM-1	1.32 (0.86 - 2.02)	0.28	0.38	1.20 (0.78 - 1.86)	0.71	0.80
Hemoglobin	0.96 (0.61 - 1.51)	0.91	0.91	1.44 (1.15 - 1.82)	0.006	0.016
IFN-gamma	0.68 (0.45 - 1.03)	0.094	0.20	0.00 (0.00 - 0.02)	<0.001	<0.001
C-reactive protein	14.39 (2.09 - 99.26)	0.004	0.021	1.02 (0.96 - 1.09)	0.52	0.62
Triglyceride	0.95 (0.90 - 1.01)	0.30	0.38	1.00 (0.99 - 1.00)	0.52	0.62

OR, odd ratio; FDR, false discovery rate.

IGFBP-1, insulin-like growth factor-1; IGFBP-2, insulin-like growth factor-2; MMP-2, matrix metalloproteinase-2; MMP-3, matrix metalloproteinase-3; MMP-9, matrix metalloproteinase-9; VEGF-A, vascular endothelial growth factor-A; BMP-9, bone morphogenetic protein-9; FABP-4, Fatty Acid-Binding Protein 4; KIM-1, Kidney Injury Molecule-1; IFN, interferon.

The multivariable model included variables measured in the adult period (i.e., age, body mass index [or waist and height ratio], metabolic syndrome, hypertension, diabetes mellitus, systolic blood pressure and total cholesterol).