Pericardial adipose tissue, cardiac structures, and cardiovascular risk factors in school-age children

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Aims
We examined the associations of pericardial adipose tissue with cardiac structures and cardiovascular risk factors in children.

Methods and results
We performed a cross-sectional analysis in a population-based cohort study among 2892 children aged 10 years (2404 normal weight and 488 overweight/obese). Pericardial adipose tissue mass was estimated by magnetic resonance imaging (MRI) and indexed on height³. Left ventricular mass (LVM) and left ventricular mass-to-volume ratio (LMVR) were estimated by cardiac MRI. Cardiovascular risk factors included android adipose tissue percentage obtained by Dual-energy X-ray absorptiometry, blood pressure and glucose, insulin, cholesterol, and triglycerides concentrations. Adverse outcomes were defined as values above the 75 percentile. Median pericardial adipose tissue index was 3.6 (95% range 1.6–7.1) among normal weight and 4.7 (95% range 2.0–8.9) among overweight children. A one standard deviation (1 SD) higher pericardial adipose tissue index was associated with higher LMVR [0.06 standard deviation scores, 95% confidence interval (CI) 0.02–0.09], increased odds of high android adipose tissue [odd ratio (OR) 2.08, 95% CI 1.89–2.29], high insulin concentrations (OR 1.17, 95% CI 1.06–1.30), an atherogenic lipid profile (OR 1.22, 95% CI 1.11–1.33), and clustering of cardiovascular risk factors (OR 1.56, 95% CI 1.36–1.79). Pericardial adipose tissue index was not associated with LVM, blood pressure, and glucose concentrations. The associations showed largely the same directions but tended to be weaker among normal weight than among overweight children.

Conclusion
Pericardial adipose tissue is associated with cardiac adaptations and cardiovascular risk factors already in childhood in both normal weight and overweight children.

Keywords
Epidemiology • Pericardial adipose tissue • Cardiovascular risk factors • Paediatrics

Introduction
Pericardial adipose tissue is a metabolically active fat depot and consists of epicardial and paracardial adipose tissue.¹ Two large prospective cohort studies in adults reported associations of larger pericardial adipose tissue volumes with the incidence of cardiovascular events, such as myocardial infarction, angina pectoris, heart failure, stroke, and death, up to a 12-year follow-up period.²,³ Also, in adults pericardial adipose tissue seems to be associated with increased left ventricular mass (LVM) and left ventricular mass-to-volume ratio (LMVR), a measure of concentricity, higher blood pressure, higher lipid concentrations, and impaired fasting glucose.²–⁴

Cardiovascular risk factors track from childhood into adulthood, suggesting that cardiovascular disease and mortality have their origins...
in early life.5–7 Whether pericardial adipose tissue contributes to development of cardiovascular risk factors from early life onwards is unknown. Studies in children suggest that epicardial adipose tissue is generally higher in obese children.6,9 Also, studies in children suggest that greater epicardial adipose tissue is associated with larger LVM, higher blood pressure and an atherogenic lipid profile.9–11 We hypothesized that pericardial adipose tissue is, independently of general adiposity, associated with cardiac measures and with cardiovascular risk factors from childhood onwards in both normal weight and overweight children.

We examined, in a population-based cohort study among 2892 school-aged children, the cross-sectional associations of pericardial adipose tissue measured with magnetic resonance imaging (MRI) with cardiac structures and with cardiovascular risk factors. Main outcomes included LVM and LMVR both measured with cardiac MRI (cMRI), android adipose tissue percentage obtained by Dual-energy X-ray absorptiometry, blood pressure and serum glucose, insulin, cholesterol, and triglycerides concentrations.

Methods

Design and study population

This cross-sectional study was embedded in the Generation R Study, a population-based prospective cohort study from foetal life onwards in Rotterdam, The Netherlands.12 Childhood anthropometrics and cardiovascular risk factors were assessed at the median age of 9.9 years (95% range 9.5–11.8 years), followed by a second visit for MRI within 1.1 months (95% range 0–24.8 months). In total, 4135 singleton born children participated in the MRI substudy, of whom 2892 had measures of pericardial adipose tissue and anthropometrics and no cardiac abnormalities.12 This lower number of pericardial adipose tissue imaging is explained by logistic issues, such as coil problems or time constraints. Of this group of children, 89% (2579) had successful cardiac measures. Missing data were mainly due to low image quality. Of the 2892 children, 72% (2069) had metabolic measures from blood samples available. Missing blood samples were mainly due to non-consent for venous puncture (flowchart, Supplementary data online, Figure S1). Written informed consent was obtained from all parents of participants. The study has been approved by the local medical ethics committee.

Anthropometrics and pericardial adipose tissue

All measurements were performed in a dedicated research centre according to research protocols. We measured child height and weight without shoes and heavy clothing. Height was measured to the nearest millimetre by a stadiometer (Holtain Limited, Crosswell, Crymlyn, UK). Weight was measured to the nearest gram using an electronic scale (SECA 888, Almere, The Netherlands), and body mass index (BMI) (kg/m²) was calculated. We obtained sex- and age-specific BMI standard deviation scores (SDS) based on Dutch reference growth curves.13 Children’s weight status was defined according to age- and sex-specific cut-off points proposed by the International Obesity Task Force.14 Body surface area (BSA) was calculated using the Haycock formula.15

Pericardial adipose tissue was measured by MRI, as described previously.12,16 Briefly, pericardial adipose tissue imaging in short-axis orientation was performed using an electrocardiogram (ECG) triggered black-blood prepared thin slice single-shot fast spin-echo acquisition with multi-breath-hold approach. Images were analysed by the Precision Image Analysis company (PIA, Kirkland, WA, USA), using the sliceOMatic (TomoVision, Magog, Quebec, Canada) software package. Inter- and intraobserver reproducibility was calculated in 25 subjects. Interobserver mean difference was 0.0 mL (standard deviation [SD] 2.9), limits of agreement -5.6 to 3.7 mL, mean value 18.2 mL (SD 6.7), and coefficient of variation was 15.8%. Intraobserver mean difference was 0.1 mL (SD 2.0), limits of agreement -3.71 to 3.96 mL, mean value 17.8 mL (SD 6.8), and coefficient of variation was 11.0%. Pericardial adipose tissue included both epicardial- and paracardial fat directly attached to the pericardium, ranging from the apex to the left ventricular outflow tract. Fat masses were obtained by multiplying the total volumes by the specific gravity of adipose tissue, 0.9 g/mL.17 Pericardial adipose tissue index was calculated as pericardial adipose tissue mass/height², the exponent was derived from a log–log regression analysis.18

Cardiac MRI

Cardiac measures were obtained by cMRI, as described previously.19 Briefly, we acquired localize images, followed by ECG gated breath-held scans for two-chamber and four-chamber views. A short-axis SSFP cine stack was then obtained with basal slice alignment with contiguous 8-mm thick slices over several end expiration breath-holds. Off-line image analyses for right and left ventricular measures on the short-axis cine stack was performed by Precision Image Analysis (Kirkland, WA, USA), using Medis QMASS software (Medis, Leiden, The Netherlands), following the guidelines of the Society for Cardiovascular Magnetic Resonance (SCMR).20 Papillary muscle was included in the ventricular cavity. Main outcomes were LVM and LMVR, LMVR was calculated as LVM/LVEDV and considered as a marker of concentric remodelling. Secondary outcomes included right end-diastolic volume (RVEDV), right ventricular ejection fraction (RVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular ejection fraction (LVEF).

Cardiovascular risk factors

Total and trunk (android) fat mass were measured using DXA (IDEXA, GE-Lunar, 2008, Madison, WI, USA), and analysed with the enCORE software v.12.6.21 Android adipose tissue percentage was calculated as android fat mass/total fat mass and used as a proxy for waist circumference. Systolic blood pressure and diastolic blood pressure were measured on the right brachial artery four times, using the validated automatic sphygmomanometer Accutror Plus (Datascope Corporation, Fairfield, NJ, USA). We used the mean values of the last three measurements in our analyses. Non-fasting blood samples were collected to measure serum glucose, insulin, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides concentrations. Glucose, total cholesterol, HDL cholesterol, and triglycerides concentrations were measured using the c702 module on the Cobas 8000 analyzer. Insulin was measured with electrochemiluminescence immunoassay (ECLA) on the E411 module (Roche, Almere, The Netherlands).22 We defined children with clustering of cardiovascular risk factors, using the previously described definition of childhood metabolic syndrome phenotype.23 Clustering of cardiovascular risk factors means having three or more of the following components: android fat mass % >75th percentile, systolic or diastolic blood pressure >75th percentile, HDL cholesterol <25th percentile or triglycerides >75th percentile, and insulin level >75th percentile.24 Percentiles were derived from the study population. We describe HDL cholesterol <25th percentile or triglycerides >75th percentile as an atherogenic lipid profile.
Covariates

Child ethnicity was classified by the countries of birth of the parents and was categorized as Dutch or non-Dutch.12 Child sex was obtained from midwife and hospital registries at birth.

Statistical analysis

First, we compared characteristics between normal weight and overweight/obese children using one-way analysis of variance tests, Mann–Whitney U test and \( \chi^2 \) test. Underweight children (n = 191) were classified as having normal weight, this clustering of weight groups did not affect our analyses. We combined overweight and obese children in one group and referred to them as overweight. Analyses were performed in the total group and in strata of normal weight (n = 2404) and overweight children (n = 488) to examine the effects and the possible interactions with BMI. Second, we used linear regression models to assess the associations of pericardial adipose tissue index with cardiac measures (LVM, LMVR, RVEDV, RVEF, LVEDV, and LVEF), and with cardiovascular risk factors (android adipose tissue percentage, systolic and diastolic blood pressures and glucose, insulin, total cholesterol, HDL cholesterol, and triglycerides concentrations). We constructed BSA-adjusted SDS for the cardiac measures using Generalized Additive Models for Location, Size and Shape (GAMLSS) in R, version 3.2.0 (R Core Team, Vienna, Austria). These models enable flexible modelling, taking into account the distribution of the outcome variable.24 Since LMVR is usually not normalized on BSA, we created SDS as (observed value-mean)/SD. Models were adjusted for age, sex, ethnicity, and time difference between the two visits. Finally, we used logistic regression models to assess the associations of pericardial adipose tissue index with adverse outcomes (high android adipose tissue percentage, high blood pressure, high insulin concentrations, atherogenic lipid profile, and clustering of cardiovascular risk factors). The statistical interaction of pericardial adipose tissue index with childhood BMI was tested by including the product term of these variables in the models. To enable comparison of effect estimates, we created SDS for all continuous determinant and outcomes variables. We did not observe significant statistical interaction terms between child sex and pericardial adipose tissue index in relation to cardiovascular measures. Since our outcomes are correlated, we considered Bonferroni correction for multiple testing too strict. To enable interpretation of level of statistical significance, we present P-values as both \( P < 0.05 \) and \( P < 0.01 \). Missing data of covariates were imputed using multiple imputations. Five data sets were created and analysed together.25 All analyses were performed using the Statistical Package for the Social Sciences version 21.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Subject characteristics

Table 1 shows that the median pericardial adipose tissue index was 3.6 (95% range 1.6–7.1) among normal weight children and 4.7

| Table 1 | Child characteristics |
|---------|-----------------------|
|         | N | Normal weight | N | Overweight | P-value |
| Age at MRI (years) | 2404 | 9.9 (9.4–11.8) | 488 | 10.0 (9.5–11.8) | 0.28 |
| Male gender, N | 2404 | 1212 (50.4) | 488 | 206 (42.2) | <0.01 |
| Ethnicity, non-Dutch, N | 2358 | 831 (35.2) | 476 | 278 (58.4) | <0.01 |
| Height (cm) | 2404 | 141.1 (6.5) | 488 | 144.3 (6.9) | <0.01 |
| Weight (kg) | 2404 | 32.6 (25.2–43.4) | 488 | 45.2 (35.3–62.7) | <0.01 |
| Body mass index (kg/m²) | 2404 | 16.5 (14.0–19.4) | 488 | 21.5 (19.7–27.9) | <0.01 |
| Pericardial adipose tissue (g) | 2404 | 10.0 (4.5–20.7) | 488 | 14.2 (6.4–26.7) | <0.01 |
| Pericardial adipose tissue index (g/m³) | 2404 | 3.6 (1.6–7.1) | 488 | 4.7 (2.0–8.9) | <0.01 |
| Cardiac measures | | | | | |
| Right ventricular end-diastolic volume (mL) | 2141 | 98.1 (18.5) | 438 | 111.4 (20.8) | <0.01 |
| Right ventricular ejection fraction (%) | 2141 | 58.3 (4.9) | 438 | 57.4 (4.6) | <0.01 |
| Left ventricular end-diastolic volume (mL) | 2141 | 98.6 (16.6) | 438 | 110.9 (19.2) | <0.01 |
| Left ventricular ejection fraction (%) | 2141 | 58.4 (4.5) | 438 | 58.3 (4.6) | 0.69 |
| Left ventricular mass (g) | 2140 | 47.6 (9.8) | 438 | 55.0 (10.2) | <0.01 |
| Left ventricular mass-to-volume ratio | 2139 | 0.49 (0.08) | 438 | 0.50 (0.08) | <0.01 |
| Cardiovascular measures | | | | | |
| Android adipose tissue (%) | 2389 | 3.7 (2.4–6.0) | 485 | 6.3 (3.7–8.2) | <0.01 |
| Systolic blood pressure (mmHg) | 2339 | 102.2 (7.5) | 477 | 108.4 (8.1) | <0.01 |
| Diastolic blood pressure (mmHg) | 2339 | 58.4 (6.3) | 477 | 60.0 (6.8) | <0.01 |
| Glucose (mmol/L) | 1727 | 5.3 (0.9) | 341 | 5.2 (0.8) | 0.12 |
| Insulin (pmol/L) | 1727 | 170.6 (33.8–564.1) | 336 | 257.4 (49.3–830.0) | <0.01 |
| Total cholesterol (mmol/L) | 1726 | 4.3 (0.6) | 340 | 4.4 (0.7) | <0.01 |
| HDL cholesterol (mmol/L) | 1728 | 1.5 (0.3) | 341 | 1.3 (0.3) | <0.01 |
| Triglycerides (mmol/L) | 1723 | 0.91 (0.40–2.43) | 338 | 1.15 (0.49–2.98) | <0.01 |
| Cardiovascular risk factor clustering, N | 1525 | 101 (6.6) | 300 | 125 (41.7) | <0.01 |

Values are expressed as means (SD), medians (95% range), or numbers (%), based on original, non-imputed data. P-values obtained from analysis of variance, Mann–Whitney U or \( \chi^2 \) tests.
Table 2  
Associations of childhood pericardial adipose tissue index with cardiovascular risk factors

| Cardiovascular risk factors in SDS | Total group (N = 2892) | Normal weight (N = 2404) | Overweight (N = 488) | P-value for interaction* |
|-----------------------------------|------------------------|--------------------------|---------------------|--------------------------|
| Left ventricular massd             | -0.01 (-0.04 to 0.03)  | 0.02 (-0.02 to 0.06)     | -0.02 (-0.08 to 0.05) | 0.02                      |
| Left ventricular mass-to-volume ratio | 0.06 (0.02 to 0.09)c  | 0.04 (-0.01 to 0.09)     | 0.03 (-0.05 to 0.11)  | 0.86                      |
| Android adipose tissue percentage  | 0.34 (0.31 to 0.37)c  | 0.19 (0.16 to 0.22)c     | 0.12 (0.06 to 0.18)c  | <0.01                     |
| Systolic blood pressure            | 0.02 (-0.02 to 0.06)  | 0.03 (-0.02 to 0.08)     | 0.00 (-0.08 to 0.08)  | 0.34                      |
| Diastolic blood pressure           | 0.01 (-0.03 to 0.05)  | 0.01 (-0.04 to 0.06)     | 0.02 (-0.07 to 0.10)  | 0.82                      |
| Glucose concentrations             | -0.02 (-0.06 to 0.01) | -0.01 (-0.06 to 0.04)    | 0.01 (-0.07 to 0.08)  | 0.60                      |
| Insulin concentrations             | 0.05 (0.01 to 0.10)d  | 0.00 (-0.05 to 0.05)     | 0.00 (-0.10 to 0.09)  | 0.15                      |
| Total cholesterol concentrations   | 0.10 (0.05 to 0.14)c  | 0.08 (0.03 to 0.14)c     | 0.07 (-0.03 to 0.17)  | 0.25                      |
| HDL cholesterol concentrations     | -0.06 (-0.11 to -0.02)c | -0.01 (-0.06 to 0.05) | 0.00 (-0.10 to 0.09) | 0.06                      |
| Triglycerides concentrations       | 0.13 (0.10 to 0.17)c  | 0.06 (0.01 to 0.12)d     | 0.16 (0.06 to 0.25)d  | 0.07                      |

Values are linear regression coefficients (95% confidence interval). The estimates represent differences in SDS of the cardiovascular measures per increase of one SDS of childhood pericardial adipose tissue index. Models are adjusted for child age, sex, ethnicity, and time difference between measurement of anthropometrics and pericardial adipose tissue.

N, number; SDS, standard deviation scores.

*P-value for interaction represents the P-value of the interaction term of pericardial adipose tissue with age and gender standardized childhood BMI.

Table 3  
Associations of pericardial adipose tissue index with clustering of cardiovascular risk factors

| Cardiovascular measures in SDS | Total group (N = 2892) | Normal weight (N = 2404) | Overweight (N = 488) | P-value for interaction* |
|--------------------------------|------------------------|--------------------------|---------------------|--------------------------|
| High android adipose tissue percentage | N = 2874 | 2.08 (1.89–2.29)b | 1.65 (1.43–1.90)b | 1.53 (1.19–1.97)b | 0.87 |
| High blood pressure             | N = 2549 | 1.04 (0.95–1.12) | 1.01 (0.92–1.12) | 1.05 (0.89–1.24) | 0.50 |
| High insulin                    | N = 2063 | 1.17 (1.06–1.30)b | 1.04 (0.91–1.19) | 1.04 (0.86–1.27) | 0.19 |
| Atherogenic lipid profile        | N = 2063 | 1.22 (1.11–1.33)b | 1.06 (0.94–1.19) | 1.28 (1.05–1.57)c | 0.05 |
| Cardiovascular risk factor clustering | N = 1825 | 1.56 (1.36–1.79)b | 1.14 (0.91–1.44) | 1.23 (0.99–1.52) | 0.04 |

Values are odds ratio’s (95% confidence interval) that reflect the risk of high (>75th percentile) android adipose tissue percentage; high (>75th percentile) systolic or diastolic blood pressure; high (>75th percentile) insulin concentration; atherogenic lipid profile (>75th percentile triglycerides or <25th percentile HDL); and the risk for having clustering of three or more risk factors, per SDS change in pericardial adipose tissue index. Models are adjusted for child age, sex, ethnicity, and time difference between measurement of cardiovascular measures and pericardial adipose tissue index.

*P-value for interaction represents the P-value of the interaction term of pericardial adipose tissue with age and gender standardized childhood BMI.

(95% range 2.0–8.9) among overweight children. As compared with normal weight children, overweight children also had a higher LVM, higher android adipose tissue percentage, higher blood pressure, higher insulin concentrations, lower HDL cholesterol concentrations, and higher triglycerides concentrations (all P < 0.01). Clustering of cardiovascular risk factors was observed in 6.6% of normal weight children and 4.17% of overweight children.

Pericardial adipose tissue, cardiac measures, and cardiovascular risk factors

Table 2 shows that in the full group, a one standard deviation (1 SD) higher pericardial adipose tissue index was associated with higher LVMR [0.06 SDS, 95% confidence interval (CI) 0.02–0.09] but not with LVM. A 1 SD higher pericardial adipose tissue index was associated with a 0.34 SDS (95% CI 0.31–0.37) higher android adipose tissue, a 0.05 SDS (95% CI 0.01–0.10) higher insulin concentrations, 0.10 SDS (95% CI 0.05–0.14) higher total cholesterol concentrations, -0.06 SDS (95% CI -0.11 to -0.02) lower HDL cholesterol concentrations, and 0.13 SDS (95% CI 0.10–0.17) higher triglyceride concentrations. Pericardial adipose tissue index was not associated with blood pressure and glucose concentrations. As compared to the full group, the effect estimates for the associations showed largely the same directions but were weaker among normal weight than among overweight children. Pericardial adipose tissue index was associated with lower RVEDV and LVEDV in the total group (Supplementary data online, Table S1).

Pericardial adipose tissue and clustering of cardiovascular risk factors

Table 3 shows that a 1 SD higher pericardial adipose tissue index was associated with increased odds of high android adipose tissue [odds ratio (OR) 2.08, 95% CI 1.89–2.29], high insulin concentrations...
Discussion

In this cross-sectional analyses embedded in a population-based cohort study, we observed that higher pericardial adipose tissue is associated with cardiac adaptations and cardiovascular risk factors already in childhood. As compared to the full group, the effect estimates for the associations showed largely the same directions but were weaker among normal weight children than among overweight children.

Interpretation of main results

Pericardial adipose tissue is associated with cardiac disease in adults. \textsuperscript{2,26} Results from the Multi-Ethnic Study of Atherosclerosis (MESA) amongst 4234 adults showed that higher pericardial adipose tissue was associated with atherosclerotic cardiovascular events, coronary heart disease, and heart failure. \textsuperscript{5} These associations were independent of BMI, waist circumference, and hepatic fat. Pericardial adipose tissue was also associated with atrial fibrillation. \textsuperscript{26} Results from the Framingham Heart Study showed among 846 adults that the ratio between epicardial and body fat was associated with coronary artery disease, independent of obesity. \textsuperscript{27} Pericardial adipose tissue was also associated with progression of coronary artery calcium, but this association was explained by BMI or visceral adiposity. \textsuperscript{28} Findings from these studies in adults suggest that pericardial adipose tissue is associated with cardiac remodelling. \textsuperscript{2,29} Also, pericardial adipose tissue among adults is associated with numerous cardiovascular and metabolic risk factors, such as insulin resistance, atherogenic lipid profile, hypertension, and metabolic syndrome. \textsuperscript{4,30} Cardiovascular risk factors track from childhood into adulthood suggesting that cardiovascular disease and mortality have their origins in early life. \textsuperscript{5,27} To the best of our knowledge, no previous studies focused on the associations of pericardial adipose tissue with cardiac structure and cardiovascular risk factors in childhood in the general population.

In this study, we examined the cross-sectional associations of childhood pericardial adipose tissue index with cardiac measures and cardiovascular risk factors among both normal weight and overweight children. We observed that both pericardial adipose tissue index and cardiac measures were larger in overweight children than in normal weight children. However, pericardial adipose tissue index was not associated with the BSA-standardized cardiac dimensions. In childhood, one of the main determinants of cardiac size is lean body mass. \textsuperscript{31} Since we were interested in the association of pericardial adipose tissue with cardiac measures independent of body size, we used BSA-standardized measures. \textsuperscript{32} Direct comparison with other studies is difficult since these studies used different methods to take into account body size. In adults, associations of pericardial adipose tissue have been observed with larger LVEDV and LVM. \textsuperscript{2,23} In children, epicardial adipose tissue was associated with larger LVM, but these studies took only height and not weight into account. \textsuperscript{8,10,11} LVMR is the ratio between LVEDV and LVM and is generally not standardized or indexed on body size. It reflects left ventricular concentricity and is associated with cardiovascular disease additional to left ventricular hypertrophy. \textsuperscript{33} We observed that pericardial adipose tissue index was associated with increased LVMR. The absence of a similar relationship in strata of normal weight and overweight children suggests that general adiposity may at least partly explain this association.

The mechanisms by which obesity affects cardiac morphology are still unclear. A study focusing on body fat distribution shows that adults with relatively more visceral fat show a larger increase in LVM than in LVEDV, thus resulting in concentric remodelling. \textsuperscript{34} Different depots of adipose tissue might influence cardiac morphology through different mechanisms. Visceral adipose tissue can affect cardiac morphology through endocrine and immune responses that affect cardiac morphology directly and through worsening of other cardiovascular risk factors. \textsuperscript{35} Pericardial adipose tissue might have an additional effect, because of its direct proximity to the myocardium. \textsuperscript{2} Obesity is associated with increased subepicardial fat, and this excess tissue can infiltrate the myocardium, changing myocardial structure. \textsuperscript{36} In patients with coronary artery disease, perivascular adipose tissue has been shown to release inflammatory factors that could influence insulin resistance and cardiovascular functioning. \textsuperscript{37} Pericardial fat-releasing inflammatory factors in proximity to the pulmonary vein ostia may trigger atrial fibrillation. \textsuperscript{38} Through these pathways, increased pericardial adipose tissue could increase the risk for cardiac disease, additional to the effects of general or visceral adipose tissue.

In obese children, epicardial adipose tissue was a good indicator of visceral fat but no independent association of epicardial adipose tissue thickness with insulin resistance and metabolic syndrome was observed. \textsuperscript{39} In line with these studies, we observed no association of pericardial fat tissue with blood pressure, nor with glucose, insulin, and HDL-cholesterol concentrations in the strata for normal weight and overweight children. In contrast to findings from a study among obese children but in line with the study among adults, we did observe associations of pericardial adipose tissue with other components of metabolic syndrome among both normal weight and overweight children. \textsuperscript{3} A previous study among adults reported that epicardial thickness was a better predictor for coronary artery disease and metabolic syndrome among adults with a normal BMI than in adults with obesity. \textsuperscript{40} In line with these results, we observed a stronger association of pericardial adipose tissue index with android adipose tissue percentage among normal weight children but not with the other cardiovascular risk factors. Additionally, we observed slightly stronger effect estimates for the associations of pericardial adipose tissue index with atherogenic lipid profile and cardiovascular risk clustering among overweight children. In our study, we observed the strongest association of pericardial adipose tissue index with android adipose tissue percentage. Android adipose tissue percentage is correlated to waist circumference. In line with these results, waist circumference in both adults and children correlated strongly with epicardial and pericardial adipose tissue. \textsuperscript{2,8,41} We observed stronger associations of pericardial adipose tissue with total cholesterol and triglycerides concentrations, than of pericardial adipose tissue with other metabolic syndrome components. This difference may be explained by the differences in mechanisms underlying the associations of pericardial adipose tissue with specific risk factors. These mechanisms need to be further studied.
Based on our results, we cannot draw conclusions whether pericardial adipose tissue is merely a marker for adiposity, or leads to additional cardiovascular risk. However, we can conclude that higher pericardial adipose tissue in childhood is associated with an adverse cardiovascular risk profile on top of its association with body weight. In adults, visceral fat and pericardial adipose tissue can be reduced by a combination of diet and exercise.\(^{32}\) Future studies are needed to assess the long term consequences of higher pericardial adipose tissue index and the reversibility in childhood and cardiovascular disease in later life.

**Methodological considerations**

Main strengths of this study are its population-based design and the large number of detailed measurements of adiposity and cardiac imaging. Some limitations need to be discussed. We did not obtain successful imaging in all participating children in this study. This could have resulted in selection bias if larger pericardial or general adipose tissue volume was related to success rate of cMRI. However, we did not observe an association between BMI and success rate of cMRI (results not shown). Since the pericardium is difficult to distinguish with our imaging method, we measured pericardial adipose tissue, which consists of both epicardial and paracardial adipose tissue. These adipose depots have different origins and might have different effects on cardiovascular disease.\(^{43}\) Epicardial fat is metabolically active and can interact directly with the myocardium, whereas paracardial fat is more likely to interact with coronary arteries.\(^{33}\) We collected non-fasting blood samples. This could have affected variation of glucose, insulin and triglycerides concentration and led to attenuation of any associations of pericardial adipose tissue with variation of glucose, insulin and triglycerides.

Our results suggest that among both normal weight and obese children, higher pericardial adipose tissue is associated with cardiac remodeling and dysfunction in childhood obesity: a cardiovascular magnetic resonance study.\(^ {11} \)

**Conclusion**

Our results suggest that among both normal weight and obese children, higher pericardial adipose tissue is associated with cardiac adaptations and cardiovascular risk factors. Further follow-up studies are needed to assess the causality of the observed associations and to assess whether pericardial fat in childhood predicts cardiovascular disease later life independent of general adiposity markers.

**Supplementary data**

Supplementary data are available at European Heart Journal - Cardiovascular Imaging online.

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**References**

1. Lavie CJ, Oktay AA, Pandey A. Pericardial fat and CVD: is all fat created equally? JACC Cardiovasc Imaging 2017; 10:1028–30.
2. Shah RV, Anderson A, Ding J, Budoff M, Rider O, Petersen SE et al. Pericardial, but not hepatic, fat by CT is associated with CV outcomes and structure: the multi-ethnic study of atherosclerosis. JACC Cardiovasc Imaging 2017; 10:1016–27.
3. Britton KA, Massaro JM, Murabito JM, Kregger BE, Hoffmann U, Fox CS. Body fat distribution, incident cardiovascular disease, and, and cause–mortality. J Am Coll Cardiol 2013; 62:921–5.
4. Rosito GA, Massaro JM, Hoffmann U, Ruberg FL, Mahabad AA, Vasan RS et al. Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. Circulation 2008; 117:605–13.
5. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 2008; 117:3171–80.
6. Joshi SM, Katre PA, Kumaran K, Jogelker C, Oomcon C, Bhut DS et al. Tracking of cardiovascular risk factors from childhood to young adulthood—the Pune Children's Study. Int J Cardiol 2014; 175:176–8.
7. Schiekem RM, Schwartz PF, Goble MM. Tracking of left ventricular mass in children: race and sex comparisons: the MCV Twin Study. Circulation 1998; 97:1901–6.
8. Cabrera-Rego JO, Iacobellis G, Castillo-Herrera JA, Valiente-Mustelier J, Cardarilla-Sarmiento JC, Marin-Julia SM et al. Epicardial fat thickness correlates with carotid intima-media thickness, arterial stiffness, and cardiac geometry in children and adolescents. Pediatr Cardiol 2014; 35:450–6.
9. Schusterova I, Leenen FH, Jurko A, Sabol F, Takacova J. Epicardial adipose tissue and cardiometabolic risk factors in overweight and obese children and adolescents. Pediatr Obes 2014; 9:63–70.
10. Ozdemir O, Hizli S, Abaci A, Aaglioglu K, Alyos S. Echocardiographic measurement of epicardial adipose tissue in obese children. Pediatr Cardiol 2010; 31:853–60.
11. Jing L, Binley CM, Suerve JD, Umsankar N, Haggerty CM, Rich J et al. Cardiac remodeling and dysfunction in childhood obesity: a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 2016; 18:28.
12. Kooijman MN, Kruthof CJ, van Duijn CM, Duijts L, Franco OH, van IMH et al. The Generation R Study: design and cohort update 2017. Eur J Epidemiol 2016; 31:1243–64.
13. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E et al. Continuing positive secular growth change in the Netherlands 1955–1997. Pediatr Res 2000; 47:316–23.
14. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000; 320:1240–3.
15. Lopez L, Colan SD, Frommeldt PC, Ensing GJ, Kendall K, Younoszai AK et al. Recommendations for quantification methods during the performance of a pediatric echocardiogram: a report from the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council. J Am Soc Echocardiogr 2010; 23:576–7: quiz 465–95.
16. Monnerneau C, Santos S, van der Lugt A, Jaddoe VVV, Felix JF. Associations of adult genetic risk scores for adiposity with childhood abdominal, liver and pericardial fat assessed by magnetic resonance imaging. Int J Obes 2018; 42:897–904.
17. Hu HH, Nayak KS. Quantification of absolute fat mass using an adipose tissue reference signal model. J Magn Reson Imaging 2008; 28:1483–91.
18. Wells JC, Cole TJ; ALSPAC study team. Adjustment of fat-free mass and fat mass for height in children aged 8 y. Int J Obes 2002;26:947–52.
19. Toemen L, Gaillard R, Roest AA, van der Geest RJ, Steegers EA, van der Lugt A et al. Fetal and infant growth patterns and left and right ventricular measures in childhood assessed by cardiac MRI. Eur J Prev Cardiol 2019;27:63–74.
20. Schulz-Menger J, Bluemke DA, Bremerich J, Flamm SD, Fogel MA, Friedrich MG et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of trustees task force on standardized post processing. J Cardiovasc Magn Reson 2013;15:35.
21. Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD et al. Multiple energy X-ray absorptiometry for quantification of visceral fat. Obesity (Silver Spring) 2012;20:1313–8.
22. Jaddoe VW, Bakker R, van Duijn CM, van der Heijden AJ, Lindemans J, Mackenbach JP et al. The Generation R Study Biobank: a resource for epidemiological studies in children and their parents. Eur J Epidemiol 2007;22:917–23.
23. Jaddoe VW, de Jonge LL, Hofman A, Franco OH, Steegers EA, Gaillard R. First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study. BMJ 2016;348:g114.
24. Rigby RA, Stasinopoulos DM. Generalized additive models for location, scale and shape. J R Stat Soc Ser C Appl Stat 2005;54:507–54.
25. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 2009;338:b2393.
26. Heckbert SR, Wiggins KL, Blackshear C, Yang Y, Ding J, Liu J et al. Pericardial fat volume and incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis (MESA). JACC Cardiovasc Imaging 2010;3:266–74.
27. Lee BC, Lee WJ, Lo SC, Hsu HC, Chien KL, Chang YC et al. The ratio of epicardial fat to body fat improves the prediction of coronary artery disease beyond calcium and Framingham risk scores. Int J Cardiac Imaging 2016;32:117–27.
28. Lee JJ, Pedley A, Hoffmann U, Massaro JM, O’Donnell CJ, Benjamin EJ et al. Longitudinal associations of pericardial and intrathoracic fat with progression of coronary artery calcium (from the Framingham Heart Study). Am J Cardiol 2018;121:162–7.
29. Fox CS, Gona P, Hoffmann U, Porter SA, Salton CJ, Massaro JM et al. Pericardial fat, intrathoracic fat, and measures of left ventricular structure and function: the Framingham Heart Study. Circulation 2009;119:1586–91.
30. Iacobellis G, Ribaudo MC, Assael F, Vecchi E, Tiberti C, Zappaterreno A et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab 2003;88:5163–8.
31. Daniels SR, Kimball TR, Morrison JA, Khoury P, Witt S, Meyer RA. Effect of lean body mass, fat mass, blood pressure, and sexual maturation on left ventricular mass in children and adolescents. Statistical, biological, and clinical significance. Circulation 1995;92:3249–54.
32. Foster BJ, Gao T, Mackie AS, Zemel BS, Ali H, Plat Js et al. Limitations of expressing left ventricular mass relative to height in body surface area in children. J Am Soc Echocardiogr 2013;26:410–8.
33. Tsao CW, Gona PN, Salton CJ, Chuang PL, Levy D, Manning WJ et al. Left ventricular structure and risk of cardiovascular events: a Framingham Heart Study cardiac magnetic resonance study. J Am Heart Assoc 2015;4:e002188.
34. Neeland JJ, Gupta S, Ayers CR, Turer AT, Rame JE, Das SR et al. Relation of regional fat distribution to left ventricular structure and function. Circ Cardiovasc Imaging 2013;6:800–7.
35. Turkbey EB, McClelland RL, Kornmal RA, Burke GL, Bild DE, Tracy RP et al. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). JACC Cardiovasc Imaging 2010;3:266–74.
36. Shrani J, Bereczkowski K, Roberts WC. Quantitative measurement of normal and excessive (cor adipsum) subepicardial adipose tissue, its clinical significance, and its effect on electrocardiographic QRS voltage. Am J Cardiol 1995;76:414–8.
37. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biometric and clinical relationships with the heart. Nat Rev Cardiol 2005;2:356–43.
38. Al-Rawahi M, Proietti R, Thanassoulis G. Pericardial fat and atrial fibrillation: epidemiology, mechanisms and interventions. Int J Cardiol 2015;195:98–103.
39. Mazur A, Ostasıks M, Telega G, Malecka-Tendera E. Is epicardial fat a marker of metabolic syndrome in obese children? Atherosclerosis 2010;211:596–600.
40. Park J-S, Ahn S-G, Hwang J-W, Lim H-S, Choi BJ, Choi S-Y et al. Impact of body mass index on the relationship of epicardial adipose tissue to metabolic syndrome and coronary artery disease in an Asian population. Cardivosc Diabetol 2010;9:29.
41. Hartalia O, Magnusson CG, Bucci M, Kajander S, Knutsi J, Ukkonen H et al. Coronary heart disease risk factors, coronary artery calcification and epicardial fat volume in the Young Finns Study. Eur Heart J Cardiovasc Imaging 2015;16:1256–63.
42. Gepner Y, Shelef I, Schawrzfuchs D, Zelicha H, Tene L, Yaskolka Meir A et al. Effect of distinct lifestyle interventions on mobilization of fat storage pools: CENTRAL, magnetic resonance imaging randomized controlled trial. Circulation 2018;137:1143–57.
43. Iacobellis G. Epicardial and pericardial fat: close, but very different. Nat Rev Cardiol 2011;8:536–43.
44. Sidhu D, Naugler C. Fasting time and lipid levels in a community-based population. J Atheroscler Thromb 2009;16:625; author reply 6–7.
45. Siddhu D, Naugler C. Fasting time and lipid levels in a community-based population. J Atheroscler Thromb 2009;16:625; author reply 6–7.
46. Hancox RJ, Landhuis CE. Correlation between measures of insulin resistance in fasting and non-fasting blood. Diab etol Metab Syndr 2011;3:23.