Original Paper

Annals of Nutrition & Metabolism

Ann Nutr Metab 2015;66:63–71
DOI: 10.1159/000369979

Received: May 8, 2014
Accepted after revision: November 13, 2014
Published online: January 21, 2015

Serum Visfatin and Leptin in Relation to Childhood Adiposity and Body Fat Distribution: The PIAMA Birth Cohort Study

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Key Words
Visfatin · Leptin · Childhood adiposity · Anthropometry

Abstract
Background/Aims: Visfatin has been suggested as a marker of visceral adiposity. We hypothesized that visfatin, but not leptin, would be specifically associated with visceral adiposity. We investigated the relation of serum visfatin and leptin with measures of adiposity and body fat distribution in children. ***Methods:*** Serum leptin and visfatin levels were measured in 1,022 12-year-old children participating in the PIAMA birth cohort. BMI, waist, hip and upper arm circumference were available for all children. Multiple linear regression analyses were conducted to study associations between different anthropometric indices and log serum visfatin and leptin levels. ***Results:*** All anthropometric indices showed positive and strong dose-response relationships with serum leptin. Visfatin was increased only in children with a high waist-to-hip ratio. The effect size was small compared to those observed for leptin and the association was present in overweight children (n = 133) but not in normal weight children. ***Conclusion:*** Serum leptin levels strongly increased with increasing adiposity, but were not related to a specific type of fat distribution. In contrast, serum visfatin was associated only with high waist-to-hip ratio in overweight children. Based on our study we would currently not recommend visfatin as a marker of visceral adiposity in the general population of children.

Introduction

Although an individual's total fat mass predicts morbidities such as cardiovascular disease and diabetes, the anatomical distribution of adipose tissue is a strong and independent predictor of such adverse health outcomes.

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Obese individuals with most of their fat stored in visceral adipose depots generally suffer worse metabolic consequences than similarly overweight subjects with fat stored predominantly in subcutaneous sites [1, 2]. However, the exact causative mechanisms are still unknown. There is evidence that different fat depots may specifically secrete certain adipokines, which may play a central role in the pathogenesis of these metabolic disorders [3, 4].

Two adipokines (leptin and visfatin) have been determined in the present study. Leptin is an important regulator of energy metabolism and considered to be related to adiposity and metabolic disorders in adults and children [5, 6]. Adipocytes in the subcutaneous fat depot secrete higher leptin levels than those from visceral fat depots [5]. Visfatin was described in 2005 as an adipokine, which is predominantly secreted by adipocytes in the visceral fat pads and as a protein with possibly insulin-like functions [7]. However, the insulin-like properties of visfatin are controversial [8, 9] and the question whether or not visfatin is specifically secreted by visceral adipose tissue is still under debate. Evidence from later studies on associations between anthropometric measures and visfatin is inconclusive [10–17]. Most of these studies have been performed in small groups of obese children/adolescents [11, 15, 17] or adults [14] complemented with small groups of controls. The objective of the present study was to investigate how serum visfatin and leptin levels are related to different anthropometric indices of adiposity and body fat distribution in a large cohort of children recruited from the general population. We hypothesized that visfatin, but not leptin, would be specifically associated with indicators of visceral adiposity, such as waist circumference.

Materials and Methods

Study Design and Population

The PIAMA study is an ongoing, population-based birth cohort study investigating the influence of lifestyle and environmental factors on the development of asthma, allergy, and early markers of cardiometabolic health. Details of the design of the PIAMA study have been published previously [18]. The cohort consists of a large sample of children (n = 3,963) who were included prenatally in 1996/1997, and have been followed up to the age of 14 years. Data on family characteristics, lifestyle, anthropometric measures, and health outcomes were obtained in 10 waves of follow-up: 3 months of age, annually from 1 to 8 years and at 11 and 14 years of age. At 4, 8, and 12 years of age subgroups of the participating children were invited for medical examination. For the 12-year medical examination, 3,202 children were eligible and 1,520 children agreed. These children were visited at home, where anthropometric measurements were taken and non-fasting blood samples were drawn. The study protocol was approved by the Medical Ethics Committees of the participating institutes, and all participants gave written informed consent.

Assessment of Anthropometric Indices and Serum Leptin and Visfatin Levels

Different measures of adiposity and fat distribution were used as exposure variables. Body Mass Index (BMI) was used as a measure of overall adiposity; hip circumference and upper arm circumference were indicators of the amount of subcutaneous fat, whereas waist circumference and waist-to-height ratio were used as indicators of abdominal adiposity as these measures best reflect the presence of visceral fat (besides subcutaneous fat). The waist-to-hip ratio was used as an indicator of fat distribution reflecting the amount of visceral fat relative to the amount of subcutaneous fat.

During medical examination, anthropometric measurements were taken by trained research staff using calibrated measuring equipment. Children, wearing just their underwear, were weighed and measured. Weight was measured to the nearest 0.1 kg and height to the nearest 1 cm. BMI was calculated as weight divided by height squared (kg/m^2). Age and sex-specific cut off points for BMI from the International Obesity Task Force (IOTF) definition [19] were used to define overweight and obesity. Waist-circumference, to the nearest 0.1 cm, was measured midway between the lowest rib and the top of the iliac crest at the end of gentle expiration. Hip-circumference, to the nearest 0.1 cm, was measured off the trochanter major. Waist-circumference as well as hip-circumference were measured twice. The mean of the two measurements was used in the analyses. The upper arm circumference, to the nearest 0.1 cm, was measured three times on the dominant arm. The mean of these three measurements was used in the analyses. The waist-to-hip ratio was calculated as the mean waist circumference divided by the mean hip circumference, while the waist-to-height ratio was calculated as the mean waist circumference divided by the child's height; both variables were expressed as a percentage.

Blood samples were taken during the same home visit. Serum was stored at –80°C for subsequent analyses. Visfatin and leptin levels were determined in 1,022 serum samples by commercially available enzyme-linked immunosorbent assay (ELISA) according to the manufacturers' instructions (ENZO Life Sciences BVBA, Antwerpen, Belgium). The limits of detection were 0.03 ng/ml for visfatin and 0.17 ng/ml for leptin. The intra- and inter-assay coefficients of variability were 2.3–9.1 and 4.7–7.2%, respectively, for visfatin, and 4.2–7.6 and 4.4–6.7% for leptin.

Statistical Analysis

Multiple linear regression analyses were conducted with quintiles of anthropometric characteristics as independent variables and serum leptin and visfatin levels as outcome variable. The distributions of serum leptin and visfatin were right-skewed and log transformed as outcome variable. Associations were therefore presented as geometric mean ratios (GMR) with 95% confidence intervals. The skewness and kurtosis test for normality confirmed that there was no violation of the normality assumption by using log serum leptin and log serum visfatin levels in the linear regression analyses. We considered the variables gender, exact age at medical examination (in days), parental BMI, and pubertal development as potential confounders. Pubertal development was mea-

Table 1. General and anthropometric characteristics of the study population, and stratified by gender at 12-year medical examination weight, height, BMI and hip circumference were significantly higher in girls than boys, while boys had a significantly higher waist-to-hip ratio and waist-to-height ratio than girls

Characteristics	Total (n = 1,022)	Girls (n = 501)	Boys (n = 521)	Overweight (n = 133)
Age, years	12.5±0.3	12.6±0.3	12.5±0.3	12.5±0.2
Weight, kg	48.0±9.1	48.8±9.3##	47.2±9.0	62.0±7.7##
Weight-for-age SDS*	0.2±1.0	0.2±1.0	0.2±1.0	1.6±0.6##
Height, cm	159.4±7.5	159.9±7.1#	158.9±7.8	161.1±6.5##
Height-for-age SDS*	0.2±1.0	0.2±1.0	0.2±1.0	0.4±0.9##
BMI, kg/m^2	18.8±2.7	19.0±2.7#	18.6±2.6	23.8±1.9##
BMI SDS*	0.2±1.0	0.1±1.0	0.2±1.0	1.8±0.4##
Waist circumference, cm	66.3±6.7	65.9±6.5	66.6±7.0	77.9±6.8##
Hip circumference, cm	81.2±7.2	83.0±7.4##	79.6±6.6	92.4±5.7##
Upper arm circumference, cm	22.9±2.6	23.2±2.5	22.6±2.7	27.1±2.0##
Waist-to-hip ratio, %	81.6±4.6	79.5±4.2##	83.7±4.1	84.4±6.0##
Waist-to-height ratio, %	41.6±3.9	41.2±3.7##	41.9±4.1	48.4±4.2##
Maternal BMI	24.1±4.0	24.1±4.0	24.1±3.9	27.2±4.8##
Paternal BMI	25.5±3.2	25.6±3.2	25.4±3.1	28.0±3.8##
Pubertal development scale (1–5)	1.5±0.5	1.8±0.6##	1.3±0.3	1.6±0.6#
Overweight†, n (%)	133 (13.0)	62 (12.4)	71 (13.6)	133 (100.0)
Obese, n (%)	11 (1.1)	5 (1.0)	6 (1.2)	11 (8.3)

All anthropometric measures as well as parental BMI and PDS were significantly higher in overweight children than normal weight children.

* SDS = Standard deviation score (used to standardize the measure for age and sex).

† Including obesity.

Significant difference between boys and girls or normal weight and overweight children ($p < 0.05$).

Significant difference between boys and girls or normal weight and overweight children ($p < 0.01$).

sured using the Pubertal Development Scale (PDS), a validated self-report measure of pubertal status [20] that was part of the 11-year-old children's questionnaire. The PDS questions were also chosen as a standard for the questionnaires in the harmonized follow-up assessment of eleven European birth cohorts on asthma and allergies (MeDALL) [21]. We checked for effect modification by gender and overweight. In the analyses stratified by overweight, the geometric mean ratios were calculated by the inter quartile range (IQR) increase in anthropometric index, because the lowest quintiles of the anthropometric indices in the overweight group did not contain any children. The final models were adjusted for gender, age, pubertal development, and maternal BMI. Of the 1,022 children with visfatin and leptin measurements, 947 also had complete data on anthropometry and all confounders and were included in the regression analyses.

Results

Characteristics of the Study Population

Of the 1,520 children who were visited at home, 1,511 had anthropometric measurements and 1,308 children provided a blood sample. Serum samples totaling to 1,022 were available for visfatin and leptin analysis. The prevalence rate of overweight and obesity in the group of children included for leptin and visfatin analyses, was 13.0 and 1.1%, respectively, which was similar to the prevalence rate of overweight and obesity in the 1,511 children with anthropometric measurements: 12.3 and 1.1%, respectively. Table 1 shows the characteristics and anthropometric indices both for the total study population, stratified by gender, and for the overweight children. The study population contained 51% boys. t-tests revealed that weight, height, BMI, and hip circumference were significantly higher in girls than boys, while boys had a significantly higher waist-to-hip ratio and waist-to-height ratio than girls. All anthropometric measures as well as parental BMI and PDS were significantly higher in overweight children than normal weight children.

Serum Leptin and Visfatin Levels

Figure 1 shows the distribution of log-transformed serum leptin and visfatin levels for all 1,022 children. Serum leptin levels ranged from 0.74 to 43.08 ng/ml, with a right-skewed distribution. There were no samples under the

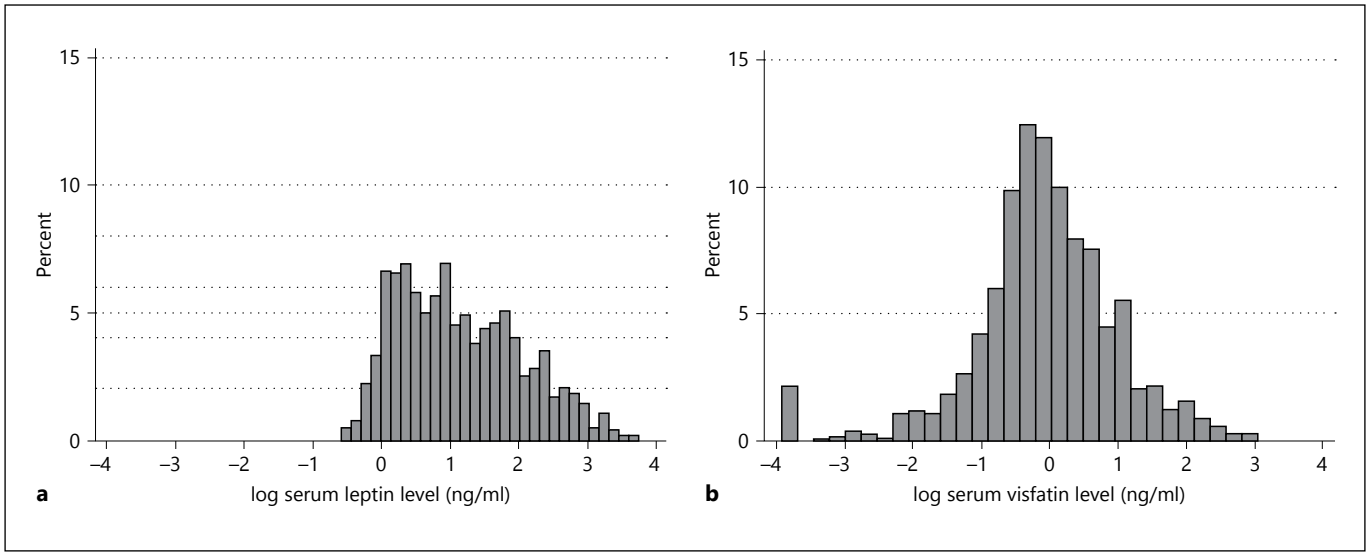

Fig. 1. Distributions of serum leptin and visfatin. Distribution of serum leptin (**a**), and distribution of serum visfatin (**b**).

detection limit of 0.17 ng/ml. Serum visfatin levels ranged from 0.02 to 21.75 ng/ml, also with a right-skewed distribution; 22 samples were under the detection limit of 0.03 ng/ml and therefore set to 2/3 of the detection limit (0.02 ng/ml). Serum leptin and visfatin levels correlated only weakly (r = 0.11).

Figure 2 shows the distributions of log-transformed serum leptin and visfatin levels separately for normal weight and overweight children. Serum leptin levels were clearly higher in overweight children than in normal weight children, whereas the ranges in log serum visfatin levels were similar for normal weight and overweight children. However, 95% of the non-detectable levels of serum visfatin were found in the group of normal weight children (21 of the 22 samples).

Associations of Serum Leptin and Visfatin Levels with Anthropometric Indices

The results of the adjusted linear regression analyses between log serum leptin and visfatin level and the different anthropometric indices are shown in tables 2 and 3. The crude associations (not shown) differed very little from the adjusted associations.

Table 2 shows that all adiposity-related anthropometric indices were significantly and positively associated with log serum leptin levels, with significant positive linear trends with increasing adiposity. The Geometric Mean Ratio (GMR) for the 5th versus the 1st quintile was >4 for each of the anthropometric indices except for the waist-to-hip ratio. For the waist-to-hip ratio, a measure of fat distribution rather than adiposity per se, the GMR (95% confidence interval (CI)) for the 5th versus the 1st quintile was 1.59 (1.34–1.91).

The associations between the anthropometric indices and visfatin levels showed a very different pattern (table 3). Visfatin levels were not associated with any of the anthropometric indices with the exception of the waist-to-hip ratio. The 5th quintile of the waist-to-hip ratio was significantly positively associated with log serum visfatin level; GMR (CI): 1.31 (1.02–1.68) (table 3), but the effect size was relatively small compared to the effect sizes observed for leptin. Analyses excluding children with visfatin levels below the detection limit showed similar results.

The analyses with serum visfatin were repeated and stratified for overweight of the child at the time of the medical examination. Table 4 shows the adjusted GMRs for the association between serum visfatin levels and the different anthropometric indices for normal weight and overweight children separately. In the normal weight children no associations were observed between the different anthropometric indices and serum visfatin level and in the overweight children only the waist-to-hip ratio was significantly associated with the serum visfatin level (GMR (CI): 1.58 (1.17–2.13) per IQR increase), with significant interaction between overweight and waist-to-hip ratio. In the overweight children positive associations with serum visfatin level were also observed for waist circumference and waist-to-height ratio, but these associations did not reach statistical significance.

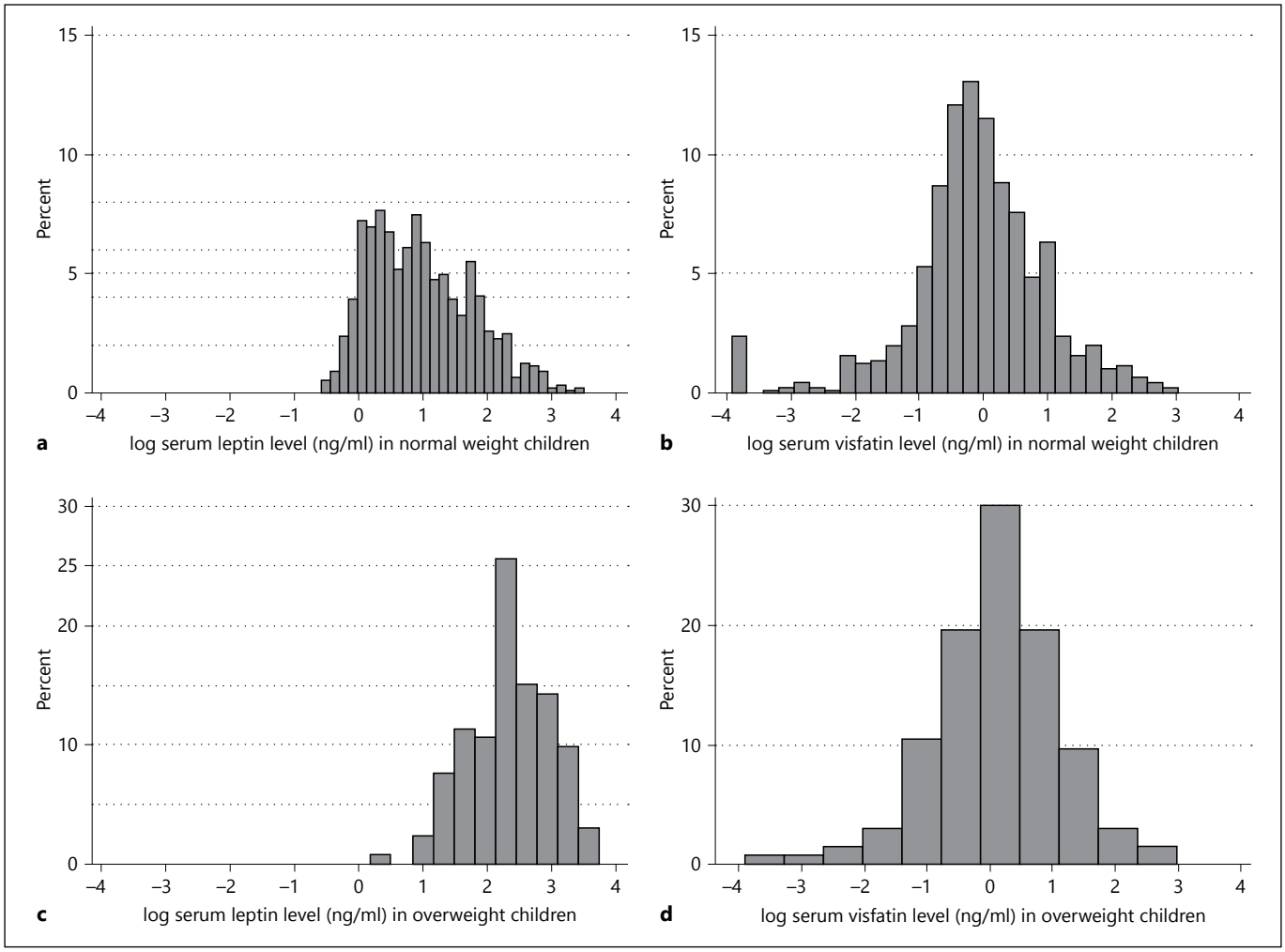

Fig. 2. Distributions of serum leptin and visfatin level (ng/ml) separate for normal weight and overweight children. Distribution of serum leptin in normal weight children (**a**), distribution of serum visfatin in normal weight children (**b**), distribution of serum leptin in overweight children (**c**), and distribution of serum visfatin in overweight children(**d**).

No interaction between gender and the anthropometric indicators was observed for either serum leptin or serum visfatin levels.

Discussion

Our results show that serum leptin levels were strongly and linearly related to all adiposity-related anthropometric indices in our study in 12-year-old children. All associations were in the same order of magnitude, except for waist-to-hip ratio which was more weakly associated than the other anthropometric indices. There was no evidence for a stronger relation of serum leptin with measures of either subcutaneous or visceral adiposity. These results are in line with earlier reports that circulating leptin levels parallel total adipose tissue mass in children, and could therefore be a useful indicator to predict the risk of developing cardiovascular disease or metabolic syndrome [6, 22–24]. Associations between the different anthropometric indices and visfatin levels showed a very different pattern than the associations with leptin levels. The serum visfatin level was not associated with any of the different adiposity measures, whereas only the association with fat distribution, indicated by the waist-to-hip ratio, was statistically significant. Stratification for overweight status showed that the significant association between the waist-to-hip ratio and the serum visfatin level was present in the overweight but not in the normal weight children. In the overweight children, there was

Table 2. Serum leptin levels by quintiles of the different anthropometric indices expressed as geometric means (GM) and geometric standard deviations (GSD), and adjusted* geometric means ratios (GMR) with 95% confidence intervals (CI)

Quintile	GM (GSD)	GMR (95% CI)
Anthropometric index		
Weight (kg)		
Q1: 25.9–40.0	1.70 (1.88)	1
Q2: 40.1–44.7	2.10 (1.96)	1.28 (1.13–1.46)
Q3: 44.8–49.4	2.84 (2.02)	1.65 (1.44–1.88)
Q4: 49.5–55.0	3.91 (2.18)	2.31 (2.02–2.64)
Q5: 55.0–87.0	7.86 (2.31)	4.31 (3.74–4.96)
Waist circumference (cm)		
Q1: 45.7–61.0	1.70 (1.81)	1
Q2: 61.1–63.7	2.21 (1.98)	1.30 (1.15–1.47)
Q3: 63.8–66.5	2.61 (2.06)	1.53 (1.35–1.74)
Q4: 66.5–70.8	3.96 (2.28)	2.26 (1.99–2.55)
Q5: 70.8–99.9	7.98 (2.17)	4.71 (4.14–5.37)
Hip circumference (cm)		
Q1: 59.3–75.0	1.54 (1.78)	1
Q2: 75.1–78.8	1.97 (1.86)	1.25 (1.12–1.42)
Q3: 78.9–82.7	2.73 (1.87)	1.73 (1.53–1.96)
Q4: 82.7–87.0	4.25 (2.06)	2.58 (2.28–2.93)
Q5: 87.0–112.8	8.94 (2.04)	5.22 (4.56–5.97)
Upper arm circumference (cm)		
Q1: 15.2–20.6	1.58 (1.86)	1
Q2: 20.7–21.9	1.97 (1.67)	1.16 (1.03–1.31)
Q3: 22.0–23.4	2.73 (1.98)	1.54 (1.37–1.74)
Q4: 23.5–25.1	4.18 (2.08)	2.28 (2.02–2.57)
Q5: 25.2–33.7	8.77 (2.13)	4.74 (4.19–5.37)
BMI (kg/m^2)		
Q1: 11.8–16.5	1.61 (1.80)	1
Q2: 16.6–17.1	1.96 (1.82)	1.23 (1.10–1.38)
Q3: 17.2–18.9	2.56 (1.97)	1.49 (1.33–1.68)
Q4: 19.0–20.7	3.95 (2.01)	2.26 (2.01–2.53)
Q5: 20.7–31.2	9.20 (1.97)	5.14 (4.57–5.79)
Waist-to-hip ratio (%)		
Q1: 68.2–77.6	4.02 (2.16)	1
Q2: 77.7–80.2	3.16 (2.43)	1.04 (0.89–1.22)
Q3: 80.3–82.6	2.61 (2.35)	0.98 (0.83–1.15)
Q4: 82.7–85.3	2.78 (2.52)	1.24 (1.04–1.47)
Q5: 85.4–99.5	3.39 (2.72)	1.59 (1.34–1.91)
Waist-to-height ratio (%)		
Q1: 30.8–38.5	1.90 (1.88)	1
Q2: 38.6–40.1	2.24 (2.04)	1.19 (1.06–1.34)
Q3: 40.2–41.5	2.58 (2.19)	1.42 (1.26–1.60)
Q4: 41.6–44.0	3.41 (2.21)	1.93 (1.71–2.18)
Q5: 44.1–60.4	8.30 (2.11)	4.48 (3.95–5.07)

* Adjusted for gender, age, pubertal development scale and maternal BMI.

Table 3. Serum visfatin levels by quintiles of the different anthropometric indices expressed as geometric means (GM) and geometric standard deviations (GSD), and adjusted* geometric means ratios (GMR) with 95% confidence intervals (CI)

Quintile	GM (GSD)	GMR (95% CI)
Anthropometric index		
Weight (kg)		
Q1: 25.9–40.0	0.91 (3.16)	1
Q2: 40.1–44.7	0.88 (2.97)	0.90 (0.73–1.12)
Q3: 44.8–49.4	0.83 (3.31)	0.87 (0.70–1.09)
Q4: 49.5–55.0	0.91 (2.78)	0.97 (0.77–1.21)
Q5: 55.0–87.0	1.20 (2.69)	1.18 (0.92–1.49)
Waist circumference (cm)		
Q1: 45.7–61.0	1.00 (2.80)	1
Q2: 61.1–63.7	0.85 (3.40)	0.80 (0.64–0.99)
Q3: 63.8–66.5	0.79 (2.88)	0.73 (0.58–0.91)
Q4: 66.5–70.8	0.99 (3.04)	0.90 (0.72–1.13)
Q5: 70.8–99.9	1.10 (2.80)	0.98 (0.78–1.24)
Hip circumference (cm)		
Q1: 59.3–75.0	0.93 (3.27)	1
Q2: 75.1–78.8	0.87 (3.10)	0.88 (0.71–1.09)
Q3: 78.9–82.7	0.88 (3.05)	0.91 (0.73–1.14)
Q4: 82.7–87.0	0.87 (3.03)	0.90 (0.72–1.14)
Q5: 87.0–112.8	1.17 (2.50)	1.12 (0.88–1.44)
Upper arm circumference (cm)		
Q1: 15.2–20.6	0.90 (3.16)	1
Q2: 20.7–21.9	0.80 (2.98)	0.88 (0.71–1.10)
Q3: 22.0–23.4	0.94 (3.28)	1.07 (0.87–1.33)
Q4: 23.5–25.1	0.92 (2.65)	0.97 (0.78–1.22)
Q5: 25.2–33.7	1.18 (2.83)	1.26 (1.00–1.58)
BMI (kg/m^2)		
Q1: 11.8–16.5	0.92 (2.92)	1
Q2: 16.6–17.1	0.84 (3.43)	0.87 (0.70–1.08)
Q3: 17.2–18.9	0.90 (2.92)	0.98 (0.79–1.23)
Q4: 19.0–20.7	0.88 (3.16)	0.90 (0.72–1.12)
Q5: 20.7–31.2	1.17 (2.52)	1.16 (0.92–1.46)
Waist-to-hip ratio (%)		
Q1: 68.2–77.6	0.92 (2.77)	1
Q2: 77.7–80.2	0.93 (2.67)	1.05 (0.84–1.31)
Q3: 80.3–82.6	0.87 (3.06)	1.01 (0.80–1.28)
Q4: 82.7–85.3	0.91 (3.03)	1.07 (0.84–1.37)
Q5: 85.4–99.5	1.07 (3.48)	1.31 (1.02–1.68)
Waist-to-height ratio (%)		
Q1: 30.8–38.5	1.06 (3.12)	1
Q2: 38.6–40.1	0.74 (2.95)	0.67 (0.54–0.83)
Q3: 40.2–41.5	0.99 (2.79)	0.91 (0.73–1.13)
Q4: 41.6–44.0	0.83 (3.15)	0.80 (0.65–1.00)
Q5: 44.1–60.4	1.11 (2.87)	0.97 (0.77–1.21)

* Adjusted for gender, age, pubertal development scale and maternal BMI.

Table 4. Adjusted* geometric means ratios between serum visfatin level and IQR increase in the different anthropometric indices stratified by overweight†

Anthropometric indices	IQR	Normal weight (n = 888) GMR (95% CI)	Overweight (n = 133) GMR (95% CI)
Weight (kg)	10.35	1.05 (0.93–1.19)	1.09 (0.83–1.42)
Waist circumference (cm)	6.30	0.99 (0.90–1.10)	1.24 (0.98–1.57)
Hip circumference (cm)	8.65	0.96 (0.84–1.09)	0.89 (0.64–1.24)
Upper arm circumference (cm)	3.05	1.09 (0.97–1.22)	1.03 (0.80–1.33)
BMI (kg/m^2)	2.75	1.04 (0.93–1.17)	1.11 (0.84–1.46)
Waist-to-hip ratio (%)	5.82	1.05 (0.93–1.18)	1.58 (1.17–2.13)
Waist-to height ratio (%)	3.28	0.98 (0.90–1.08)	1.25 (0.97–1.62)

* Adjusted for gender, age, pubertal development stage and maternal BMI. † Including obesity.

also a tendency toward positive associations for waist circumference and waist-to-height ratio and serum visfatin level, albeit not statistically significant.

Serum levels of leptin and visfatin in our study were only weakly correlated (r = 0.11) and were differently associated with anthropometric indices, supportive and in line with their hypothesized different site of production and/or role in metabolism. Visfatin might indeed be independently regulated in obesity and might be involved in the onset of metabolic derangements due to (visceral) obesity [25–27].

Our study suggests an association between a predominantly abdominal fat distribution (c.q. an anthropometric proxy thereof) and serum visfatin levels not only in overweight children, but also in the total population-based sample with a relatively modest prevalence of overweight/obesity.

Case-control studies comparing obese children to a control group, consistently showed significantly higher visfatin levels in the obese subjects compared to the control group [11, 15, 25, 26]. However, results regarding specific anthropometric indices in obese children were inconsistent. The study of Araki et al. [11] was the only study in children that objectively measured the visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) areas (in cm^2) by computed tomography. Results of this study showed that plasma visfatin levels were significantly correlated with the amount of VAT (r = 0.35) but not SAT in obese children, after adjustment for age and sex. The study of Davutoglu et al. [28] showed that log visfatin levels were significantly positively correlated to weight (r = 0.49), waist circumference (r = 0.49), hip circumference (r = 0.39), and BMI (r = 0.51) in the group of obese children, but not in the nonobese controls. The studies of Haider et al. [25] and Jin et al. [15] in children and adolescents did find higher visfatin levels in the (morbidly) obese group compared to the control group, but found no association between visfatin levels and BMI in the total study population. However, in contrast to our study, no information was obtained in those latter studies on the location of the fat depots.

In addition to the results from case-control studies in children, three small cross-sectional studies in (selected subgroups of) children were published: the study of Kim et al. [27] in 135 children and adolescents (8–16 years of age) found that in the lower-adiposity group, plasma visfatin levels were significantly correlated with total abdominal fat, visceral fat, subcutaneous abdominal fat, plasma triglyceride level, and homeostasis model assessment of insulin resistance (HOMA-IR). The study of Dedoussis et al. [23] assessed visfatin expression in adipose tissue and peripheral blood mononuclear cells (PBMC) in 31 (7- to 14-year-old)-children admitted for surgery of appendicitis, and showed a positive association between visfatin expression and BMI (beta 0.464, p = 0.006). The cross-sectional study of Kolsgaard et al. [4] in 175 overweight and obese children aged 3 to 17 years found no associations between serum visfatin levels and BMI or a high waist circumference (>90th percentile). The waist-to-hip ratio was not assessed in this group.

Also in adults, the evidence for an association between visceral adiposity and visfatin levels is limited. The study of Kaminska et al. [14] found no correlation between visfatin levels and any of the measured anthropometric parameters (BMI, weight, waist circumference, hip circumference), neither in the obese adults nor in the control group. Surprisingly, a negative correlation between visfatin levels and waist-to-hip ratio (r = –0.28, p = 0.031) was

found in the obese group. However, Berndt et al. [26] using DEXA, did find plasma visfatin levels to be correlated to BMI and % body fat in adults, but failed to observe a relation to the visceral fat mass or the waist-to-hip ratio. Sandeep et al. [12] found serum visfatin levels to be correlated to visceral fat and obesity (BMI and waist circumference) in Asian Indian adults.

The studies described above are not easy to compare or interpret, because of differences in study population and ethnicity [12], the small number of observations, case-control design, the differences in visfatin assessment (plasma visfatin, serum visfatin, or visfatin expression in adipose tissue and PBMC), and the various and sometimes limited number of anthropometric indices used. Taken together, the evidence, including our own, suggests that there may be a certain adiposity threshold above which the relationship between visfatin and (visceral) adiposity becomes apparent.

Also, visfatin may show a higher expression specifically during visceral adipose tissue expansion mainly occurring until adolescence is complete [12, 29, 30], thus possibly explaining the absence of an association in adults [14, 26].

Strong points of our study were the large study population recruited from the general population with both normal weight and overweight children, the use of several objectively measured anthropometric indices, and the fact that anthropometric measures and blood samples for visfatin and leptin analyses were taken at the same time.

As limitation of our study it should be stated that the anthropometric indices used, though cheap and noninvasive, are a crude estimate and not the most accurate way to assess the amount of visceral and subcutaneous fat tissue or its distribution. More accurate measurements of specific adipose tissue can be obtained by dual energy X-ray absorptiometry (DEXA) or CT scan. However, these methods are costly and require participants to come to a clinic, which were the reasons that it was unfeasible to do it in our study. Yet, by using the different anthropometric indices we could clearly demonstrate an association between adiposity and circulating leptin levels. We therefore believe that if there was also a clear association between (specific) adiposity and visfatin we could have found it by using the anthropometric indices as well.

In conclusion, serum leptin levels showed strong associations with all measures of adiposity in the total study population. There was no strong evidence for a relation with a specific type of fat distribution. In contrast, serum visfatin levels were associated only with the waist-to-hip ratio; this association was present only in the subgroup of overweight children and the effect size was relatively small when compared to the effect sizes observed for leptin. More studies, preferably with accurate measures of visceral fat, are needed to elucidate the association between visceral adiposity and visfatin. Currently, there seems to be insufficient evidence to consider visfatin as a marker of visceral adiposity in the general population of children.

Acknowledgments

The authors would like to thank G. Witte for determining the leptin and visfatin levels in the serum samples, and M. Oldenwening, M. Tewis and A.P.H. Wolse for coordinating the home visits and data management in the PIAMA study.

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