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Dietary calcium intake and adiposity in children and adolescents: Cross-sectional and longitudinal results from IDEFICS/I.Family cohort

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Abstract *Background and aims:* Studies in children and adolescents suggest that higher dairy consumption may exert a protective effect on adiposity. However, only few studies examined the association between dietary calcium intake and body mass measures with conflicting results. We evaluated the association between total dietary calcium, calcium from dairy and non-dairy sources and anthropometric indices in a large European cohort of children and adolescents.
Methods and Results: As many as 6,696 children belonging to the IDEFICS study were eligible for the cross-sectional analysis (Boys = 51%; age 6.0 ± 1.8 years; mean ± SD). Of these, 2,744 were re-examined six years later (Boys = 49.6%; age = 11.7 ± 1.8 years) in the framework of the I.Family study. The exposures were the baseline energy-adjusted total, dairy and non-dairy calcium intakes measured by a validated 24-h dietary recall. Multivariable linear regression was used to determine the association between calcium intake and z-scores of anthropometric indices (body mass index, BMI; waist circumference, WC; sum of skinfolds, SS; fat mass index, FMI) at baseline, and their variation over the 6 years follow-up. The association of dietary calcium with the incidence of overweight/obesity was also assessed.

At baseline, an inverse association between total calcium intake and all the adiposity indices was consistently observed in boys, while only SS and FMI were significant in girls. The prevalence of overweight/obesity decreased significantly ($P < 0.0001$) across tertiles of calcium intake, in both sexes. Over the follow-up, boys with higher baseline calcium intake value showed significantly lower increase in BMI, WC and FMI z-scores, while in girls only a lower increase in WC z-score was observed. Only in boys, the risk to become overweight/obese decreased significantly

Abbreviations: 24-HDR, 24-h dietary recall; BMI, body mass index; CI, Confidence intervals; FMI, fat mass index; GLM, General Linear Model; Non-OW, underweight plus normal weight; OW/Ob, overweight plus obese; SACINA, Self-Administered Children and Infant Nutrition Assessment; WC, waist circumference.

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across tertiles of calcium intake. Similar results were observed by analyzing only dietary calcium from dairy, while no association was observed between non-dairy calcium and adiposity indices.
Conclusions: We showed in a large cohort of European children and adolescents that dietary calcium intake may play a role in the modulation of body fat in developmental age. The association between dietary calcium and adiposity indices was driven by dairy calcium, while no effect was observed for non-dairy calcium intake. The existence of a sex-related difference in the association deserves further investigations.

Introduction

Childhood obesity is one of the most serious public health concerns of the 21st century [1]. Although a plateau in prevalence rates has been reported for several Western countries [2], it still remains a problem, given that an elevated body mass index (BMI) in childhood predicts obesity and related complications in adulthood [3]. Therefore, the identification of modifiable risk factors early in childhood is an important step to prevent lifelong diseases related to obesity.

Among modifiable risk factors, dietary habits play a key role in the onset of overweight/obesity throughout the life cycle [4,5]. While it is commonly accepted that energy balance plays a major role in maintaining body composition, a growing number of studies have explored micronutrients that, without having a caloric value, could affect adiposity [6]. Among micronutrients, calcium seems to have a key role in body weight regulation [7,8]. The most cited calcium-adiposity hypothesis was firstly advocated by Zemel et al. [9]. According to this hypothesis, a high dietary calcium intake is associated with reduced calcitriol levels which in turn decreases adipocyte calcium influx. Reduced intracellular calcium limits the storage of fat in these cells, through inhibition of lipogenesis and stimulation of lipolysis, thus reducing weight gain [9].

The role of calcium supplements or calcium-rich foods on body weight was extensively explored in adult population [10,11], while less evidence is available for children and adolescents. In particular, most of the studies in children and adolescents evaluated the association between milk and dairy consumption and adiposity measures both in cross-sectional [12] and prospective studies [13], suggesting that higher dairy consumption (in general considered as a proxy for calcium intake) may exert a protective effect on adiposity in children. However, although milk and dairy foods represent the major source of dietary calcium, particularly in children, there are other foods which contribute significant amount of dietary calcium [14]. To date, only few studies have evaluated the association between dietary calcium intake and body mass measures in children and adolescents, which yielded conflicting results [15–22].

Given the paucity of the evidence, we aimed to disentangle, in a cross-sectional and longitudinal analysis, the relative contribution of dairy and non-dairy calcium intake to the association between daily total calcium intake and anthropometric indices in the large European cohort of children and adolescents participating in the IDEFICS (Identification and prevention of dietary- and lifestyle-induced health effects in children and infants)/I.Family (Investigating the determinants of food choice, lifestyle and health in European children, adolescents and their parents) studies.

Methods

Study population

The IDEFICS baseline survey was carried out from September 2007 to May 2008, in a population-based sample of 16,228 children aged 2–9 years from eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain, Sweden); follow-up examinations were conducted six years later (I.Family study). The study design has been described in detail elsewhere [23,24].

In brief, the IDEFICS/I.Family study involved one of the largest prospective European children's cohorts. The aim of the IDEFICS study was to investigate diet- and lifestyle related disorders in young children with a focus on overweight and obesity. Since the IDEFICS study included an intervention program, in each country two comparable areas (intervention and control region) were selected [25]. Between March 2013 and April 2014 all children who participated in the IDEFICS study were invited to take part in the I.Family survey to explore the determinants of dietary and other lifestyle behaviors in children and adolescents during growth.

From the full survey sample of 16,228 children, we excluded 8,053 subjects with incomplete information on dietary intake and all required covariates, and further 228 children that used calcium or multivitamin supplements during the week before the visit From the resulting 7,947 children we further excluded 1,251 who reported implausible energy intake values. The cut-off values used to classify the 24-HDR in under-reports, plausible reports and over-reports, respectively were calculated according to Goldberg et al [26], as described in Bornhorst et al [27].

A total of 6,696 children was eligible for the cross-sectional analysis (Boys = 51%; age 6.0 ± 1.8 years; mean ± SD).

Of these, 2,744 were re-examined six years later (Boys = 49.6%; age = 11.7 ± 1.8 years). After the exclusion of 261 children for which no data on pubertal status were available, 2,483 were included in the follow-up analysis. The risk of developing overweight/obesity over the follow-up was assessed in 1,957 children who were normal weight at baseline. The participants flow chart is reported in Fig. 1.

Ethics statement

IDEFICS/I.Family studies were conducted according to the standards of the Declaration of Helsinki. The protocol was approved by the local ethics committee of each participating center carrying out the fieldwork. Participants were not subjected to any study procedure before both the children and their parents gave their oral (for children) and written (for adolescents and parents) informed consent.

Registration number: ISRCTN62310987.

Anthropometric measurements and questionnaires

Children and adolescents underwent a standardized physical examination during which body weight, height, waist circumference, and skinfolds thickness were measured. A detailed description of the anthropometric measurements, including intra- and inter-observer reliability, has been published by Stomfai et al. [28].

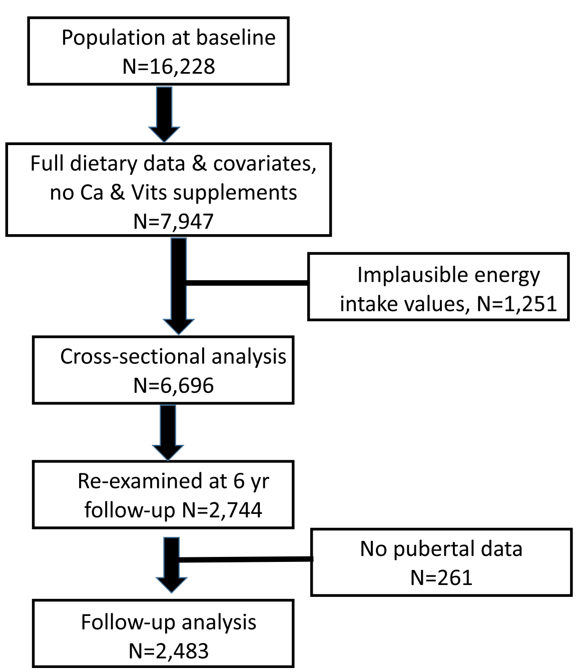

Figure 1 Participant flow chart.

The measurement of weight, to the nearest 0.1 kg, was carried out using an electronic scale (Tanita BC420SMA for children ≤6 years, BC 418 MA for children >6 years, Tanita Europe GmbH, Sindelfingen, Germany) in children wearing light clothes and without shoes. Height was measured using a telescopic height-measuring instrument (Seca 225, stadiometer, Birmingham, UK) to the nearest 0.1 cm. BMI was calculated as weight (in kg) divided by height squared (in m^2). Children were classified as normal weight, overweight or obese according to the cut-offs published by Cole and Lobstein [29]. For the purpose of the present analyses, children were grouped into two categories: Non-OW (underweight plus normal weight) and OW/Ob (overweight plus obese).

Waist circumference (WC) was measured using an inelastic tape (Seca 200 Birmingham, UK), range 0–150 cm, at the midpoint between the top of the iliac crest and the lower coastal border with the subject in a standing position and recorded at the nearest 0.1 cm.

Both triceps and subscapular skinfold thickness were measured by means of a Holtain caliper (Holtain Ltd, Pembrokeshire, UK, range 0–40 mm). Measures were taken twice on the right hand side of the body and the mean was calculated. Age- and sex-specific z-scores were calculated for the anthropometric variables included in the analysis.

The intra-observer reliability was 97.7% for skinfold thickness (triceps, subscapular, biceps, suprailiac) and 94.7% for circumferences (neck, arm, waist, hip). Inter-observer agreement as assessed by the coefficient of reliability for repeated measurements of skinfold thickness and circumferences was above 88% in all countries [28].

The sum of subscapular (mm) and triceps (mm) skinfold thicknesses was used for the calculation of body fat mass according to Slaughter et al. [30] and used for the calculation of the fat mass index (FMI). The FMI was calculated according to the following formula: [(weight in kilograms) *(fat mass percentage/100)]/(height in metres) [31].

Parents were asked to fill in a questionnaire to collect data on the participating child aged below 11 years, while for older children this information were self-reported. Participants were also invited to indicate how many minutes per day spent in outdoor activities (i.e., time spent playing in the yard or in outdoor recreation area as swimming pool, zoo and/or park) both on weekdays and weekend days. An additional question investigated whether or not they regularly attended a club to practice sport. The total weekly physical activity time was calculated as the sum of hours spent in one of these categories. Parental information was collected as well (age, self-reported weight and height, education level, and occupation). The educational level of the parents was classified in 6 categories (from 0 to 5), according to the International Standard Classification of Education (ISCED) criteria [32]. Parents with BMI ≥25 kg/m^2 were considered overweight.

The medical history of the participating child/adolescent was collected in a face-to-face interview during the

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physical examination. Parents were also asked to indicate whether their child had taken any kind of drug, mineral or vitamin supplement during the week before the physical examination. During the follow-up examination, pubertal stage (pubertal, pre-pubertal, no information available; defined based on voice change in boys and first menstrual period in girls) was evaluated.

Dietary intake assessment

Dietary intake of the previous 24-h was assessed using the computer-assisted 24-h dietary recall (24-HDR), called SACINA (Self-Administered Children and Infant Nutrition Assessment). The SACINA software was based on the YANA-C (Young Adolescents' Nutrition Assessment on Computer) system developed within the HELENA study (htpp://www.helenastudy.com) [33]. This instrument has been validated against the doubly-labeled water method with regard the total energy intake [34]. Spearman's correlations between the self-reports and the dietitians' interviews were highly significant for all nutrients and energy ranging between 0.86 and 0.91 [33]. A full description of the SACINA software can be found elsewhere [35]. In brief, parents or other caregivers as proxy respondents for recalling children's diet were asked to give information on the amount and type of foods and drinks consumed during the day before the physical examination, starting with the first intake after waking up in the morning. SACINA presented, in an interactive menu, country-specific food items with standardized photographs of different portion sizes, facilitating their estimation. SACINA was carried out on all days of the week, including weekends, in a single occasion for all participants; in a subsample (20%) it was repeated on three occasions in order to evaluate the repeatability. School meals were assessed using a standardized observer sheet which was completed by trained personnel. All dietary information was linked to country-specific Food Composition Tables in order to calculate nutrients intake.

In the present study we considered dietary calcium from dairy and non-dairy sources. Dairy products are certainly the main source of calcium during childhood, but also other foods, such as dark green leafy vegetables, beans, bottled water, breakfast cereals, and calcium-fortified juices can contribute to calcium intake. In the present analysis, to control for confounding and mitigate extraneous variation, calcium intake was adjusted for energy intake and expressed as mg per 1000 kcal consumed (energy-adjusted calcium intake), according to Willet et al. [36].

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics (Version 23.0. Armonk, NY: IBM Corp.). All analyses were performed separately in boys and girls. Data were expressed as mean and 95% confidence intervals (CI) for continuous variables and as percentages for categorical variables. Children were divided in sex-specific tertiles according to baseline energy-adjusted calcium intake.

The statistical models described below were run separately for total, dairy and non-dairy calcium intake as exposure.

Cross-sectional association analysis of calcium intake with anthropometric variables was performed using analysis of co-variance (GLM, General Linear Model). The models were adjusted for country of origin, age, physical activity, parental overweight/obesity, and parental education. *P* values for linear trend were calculated. Prevalence of overweight/obesity across the calcium intake categories was assessed by χ^2 test.

Longitudinal analyses were performed using the six years variation in the outcome adiposity variables (follow-up value minus baseline value) across the baseline calcium intake tertiles. Models were adjusted for the respective baseline value of the outcome variable of interest and for other relevant confounders (country of origin, age, physical activity, parental overweight/obesity, parental education, intervention/control study group and the individual time interval between baseline and follow-up). *P* values for linear trend were calculated.

The risk to develop overweight/obesity over the follow−up was assessed in children who were normal weight at baseline. Logistic regression analysis was performed with overweight/obesity dummy variable (developed OW/Ob or did not develop OW/Ob) as outcome and calcium intake categories as independent variable, adjusting for all covariates above mentioned and using the highest tertile as the reference group. Odds ratio and their 95% confidence intervals were calculated.

A 2-tailed *P* value less than 0.05 was considered as statistically significant.

Results

Descriptives

The characteristics of the population at baseline, and at the end of the 6-years follow-up are reported in Table 1. Girls had both a lower daily energy intake and a lower calcium intake in comparison to boys, but, when energy-adjusted calcium intake was considered, intakes were similar in both sexes.

Cross-sectional analysis

Total dietary calcium intake

Mean adiposity measures across the baseline tertiles of energy-adjusted calcium intake, after adjustment for covariates, are presented in Table 2. The prevalence of overweight/obesity decreased significantly ($P < 0.0001$) moving from the first to the third tertile of calcium intake, in both boys and girls. At multiple regression analysis, an inverse association between calcium intake and adiposity indices was consistently observed in boys, in which lower z-score values of BMI, waist circumference, sum of skinfolds and FMI were associated with higher calcium intake. In girls, a statistically significant inverse association was found only for the sum of skinfold and FMI.

Table 1 Characteristics of the sample at baseline and after 6 years.

	Baseline		Follow-up (6 yrs)	
	Boys (n = 3,417)	Girls (n = 3,279)	Boys (n = 1,232)	Girls (n = 1,251)
Age, yrs	6.0 (2.0, 9.9)	6.1 (2.0, 9.9)	11.7 (7.2, 15.9)	11.9 (7.1, 15.3)
z-score BMI	0.36 (−5.34, 5.03)	0.37 (−5.42, 4.06)	0.65 (−2.95, 3.38)	0.54 (−7.37, 3.51)
z-score WC	0.24 (−5.42, 5.19)	0.27 (−5.33, 4.74)	0.59 (−3.52, 5.00)	0.44 (−4.11, 3.89)
z-score SS	0.62 (−8.04, 8.63)	0.63 (−7.08, 8.62)	1.13 (−5.83, 6.93)	0.94 (−6.39, 7.32)
z-score FMI	0.40 (−5.15, 7.66)	0.51 (−4.77, 8.30)	0.73 (−3.58, 5.00)	0.74 (−4.01, 5.00)
Physical activity, hrs/wk	17.0 (0.0, 40.8)	16.6. (0.0, 40.5)	16.8 (1.8, 38.0)	15.1 (3.0, 37.0)
Total EI, kcal/day	1609 (588, 3604)	1486 (574, 3017)	1816 (506, 4689)	1573 (505, 6442)
Total calcium intake, mg/day	712.8 (54.8, 2800.1)	656.1 (62.9, 777.2)	657.8 (60.9, 2441.4)	591.0 (75.4, 3656.3)
Total calcium intake, mg/1000 kcal	452.3 (47.0, 1382.4)	450.2 (45.6, 1532.1)	371.2 (54.5, 1369.2)	381.9 (63.6, 1342.4)
Calcium intake from dairy, mg/1000 kcal	295.4 (0.00, 1321.3)	286.5 (0.00, 1432.9)	252.5 (8.04, 1054.0)	251.2 (6.54, 1182.6)
Calcium intake from non-dairy, mg/1000 kcal	156.9 (0.00, 830.8)	163.6 (0.00, 1012.0)	156.9 (0.00, 830.8)	163.6 (0.00, 1012.0)

Values are mean (range).
Abbreviations: BMI, body mass index; WC, waist circumference; SS, sum of skinfolds (subscapular + tricipital); FMI, fat mass index; EI, energy intake; Kcal, kilocalories.

Dairy and non-dairy calcium intake

When the association between dairy calcium intake and adiposity indices was evaluated, the results were fully superimposable to those observed for total dietary calcium, in both boys and girls (Table 2a). We also analyzed the association of calcium intake from non-dairy sources. While a trend for a reduced prevalence of overweight/obesity across tertiles of intakes was observed in both boys and girls, no significant association was observed for any of the anthropometric indices under investigation (Supplemental Table 1).

Prospective analysis

Total dietary calcium intake

Table 3 reports the changes in anthropometric variables in boys and girls over the six years follow-up across the calcium intake categories defined at baseline. Boys with higher baseline calcium intake value showed significantly lower increase in BMI, WC and FMI z-scores, while in girls only a lower increase in WC z-score was observed. Over the follow-up, 156 and 133 incident cases of overweight/obesity were observed in boys and girls, respectively. The relative risk of developing overweight/obesity over the follow-up according to baseline calcium intake is showed in Table 4. In boys, the risk to become overweight/obese decreased significantly moving from the first to the third tertile of calcium intake, after adjusting for all confounders, while in girls no significant association was observed.

Dairy and non-dairy calcium intake

Similarly to what observed for total calcium intake, higher baseline dairy calcium intake was associated, only in boys, to a lower increase in anthropometric indices over time (Table 3a), and to an increased risk to become overweight/obese (Table 4a). No significant association was observed in girls.

Table 2 Anthropometric variables in boys and girls at baseline across tertiles of total calcium intake.

	Boys				Girls			
	I (n = 1,099)	II (n = 1,136)	III (n = 1,182)	P for trend	I (n = 1,057)	II (n = 1,088)	III (n = 1,134)	P for trend
Calcium intake, mg/1000 kcal	249.2 (243.2, 255.2)	428.2 (422.4, 434.0)	664.2 (658.5, 670.0)		246.8 (240.5, 253.0)	421.5 (415.3, 427.6)	667.4 (661.3, 673.4)	
Age, yrs	6.0 (5.9, 6.1)	6.0 (5.9, 6.1)	6.0 (5.9, 6.1)	0.965	6.1 (6.0, 6.2)	6.1 (6.0, 6.2)	6.1 (6.0, 6.2)	0.949
OW/OB, %	26.1	18.7	15.7	$\chi^2 < 0.0001$[a]	25.4	21.1	18.3	$\chi^2 < 0.0001$[a]
z-score BMI	0.41 (0.33, 0.49)	0.27 (0.20, 0.35)	0.21 (0.14, 0.28)	<0.0001	0.26 (0.18, 0.33)	0.20 (0.13, 0.28)	0.19 (0.11, 0.26)	0.238
z-score WC	0.33 (0.24, 0.41)	0.21 (0.12, 0.29)	0.18 (0.10, 0.26)	0.019	0.24 (0.16, 0.32)	0.28 (0.19, 0.36)	0.29 (0.21, 0.37)	0.442
z-score SS	0.87 (0.72, 1.02)	0.56 (0.41, 0.70)	0.43 (0.29, 0.58)	<0.0001	0.80 (0.65, 0.96)	0.64 (0.49, 0.80)	0.46 (0.30, 0.61)	0.002
z-score FMI	0.56 (0.46, 0.65)	0.37 (0.27, 0.46)	0.27 (0.18, 0.37)	<0.0001	0.64 (0.53, 0.75)	0.51 (0.40, 0.62)	0.38 (0.27, 0.49)	0.002

Values are mean (95% confidence interval (CI)), adjusted for country of origin, physical activity, parental overweight/obesity, and parental education.
Abbreviations: OW/OB, prevalence of overweight/obesity; BMI, body mass index; WC, waist circumference; SS, sum of skinfolds (subscapular + tricipital); FMI, fat mass index.
[a] P by Linear-by-linear association.

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Table 2a Anthropometric variables in boys and girls at baseline across tertiles of dairy calcium intake.

	Boys				Girls			
	I (n = 1,125)	II (n = 1,131)	III (n = 1,161)	P for trend	I (n = 1,081)	II (n = 1,084)	III (n = 1,114)	P for trend
Calcium intake from dairy, mg/1000 kcal	109.6 (103.9, 115.3)	268.0 (262.4, 273.7)	502.0 (496.4, 507.6)		104.1 (98.3, 110.0)	259.5 (253.6, 265.3)	489.9 (484.1, 495.7)	
Age, yrs	6.0 (5.9, 6.1)	6.0 (5.9, 6.1)	6.0 (5.9, 6.1)	0.965	6.1 (6.0, 6.2)	6.1 (6.0, 6.2)	6.1 (6.0, 6.2)	0.949
OW/OB, %	25.3	18.8	16.0	$\chi^2 < 0.0001$[a]	23.6	23.2	18.0	$\chi^2 = 0.002$[a]
z-score BMI	0.42 (0.35, 0.49)	0.27 (0.20, 0.34)	0.20 (0.12, 0.27)	<0.0001	0.23 (0.15, 0.30)	0.27 (0.19, 0.35)	0.15 (0.07, 0.23)	0.172
z-score WC	0.35 (0.27, 0.44)	0.20 (0.11, 0.28)	0.16 (0.08, 0.24)	0.001	0.22 (0.14, 0.30)	0.33 (0.24, 0.41)	0.26 (0.17, 0.34)	0.575
z-score SS	0.90 (0.75, 1.05)	0.53 (0.38, 0.67)	0.43 (0.29, 0.58)	<0.0001	0.71 (0.56, 0.87)	0.79 (0.64, 0.95)	0.39 (0.24, 0.54)	0.003
z-score FMI	0.58 (0.48, 0.68)	0.35 (0.25, 0.44)	0.26 (0.17, 0.36)	<0.0001	0.58 (0.47, 0.69)	0.61 (0.50, 0.72)	0.33 (0.22, 0.44)	0.002

Values are mean (95% confidence interval (CI)), adjusted for country of origin, physical activity, parental overweight/obesity, and parental education.
Abbreviations: OW/OB, prevalence of overweight/obesity; BMI, body mass index; WC, waist circumference; SS, sum of skinfolds (subscapular + tricipital); FMI, fat mass index.
[a] P by Linear-by-linear association.

Prospective analysis confirmed the lack of association between calcium intake from non-dairy sources and changes in anthropometric indices (Supplemental Table 2).

Discussion

The aim of the present study was to examine, cross-sectionally and longitudinally, the relationship between dietary calcium intake, expressed as energy-adjusted calcium intake, and adiposity indices in a large and well standardized cohort of European children, and to evaluate the relative contribution of dairy and non-dairy calcium to this association.

Cross-sectional analyses revealed that lower calcium intake at baseline was associated with higher prevalence of overweight/obesity in both boys and girls. In boys, higher adiposity indices were associated with lower calcium intake, while in girls statistical significance was attained for the sum of skinfolds and FMI.

At longitudinal analyses, we reported that lower calcium intake at baseline predicted higher increase of BMI, WC and FMI z-scores over time in boys, while in girls only a significant increase in WC was observed. Of note, in boys who were normal weight at baseline lower calcium intake was associated with a significantly higher risk to develop overweight or obesity over the follow-up. No such evidence was observed in girls.

In both cross-sectional and prospective analyses, the association between dietary calcium and adiposity was driven by calcium intake from dairy sources, with no apparent effect of non-dairy calcium sources.

To date, relatively few studies have investigated the role of calcium (or calcium-rich foods) intake in modulating adiposity in young populations. Most of these studies supported an "anti-obesity" effect of calcium intake, consistent with our results, while others did not find this association [15–22].

Novotny et al. found in 9- to 14-y-old girls an inverse association between calcium from dairy foods and iliac skinfold thickness, while no association was reported for non-dairy calcium [15]. Dos Santos et al. [16] evaluated the association between total calcium intake and body fat in 47 normal weight and 49 obese post-pubertal adolescents, showing a negative association, mainly in obese girls. More recently, Keast et al. [17], analyzing the data from the National Health and Nutrition Examination Survey study,

Table 3 Changes in anthropometric variables over the 6-year follow-up across tertiles of total calcium intake defined at baseline.

	Boys				Girls			
	I (n = 392)	II (n = 420)	III (n = 420)	P for trend	I (n = 427)	II (n = 397)	III (n = 427)	P for trend
Δ z-score BMI	0.38 (0.29, 0.46)	0.28 (0.20, 0.36)	0.24 (0.15, 0.32)	0.026	0.10 (0.02, 0.18)	0.07 (−0.02, 0.15)	0.03 (−0.05, 0.11)	0.236
Δ z-score WC	0.47 (0.36, 0.59)	0.30 (0.19, 0.41)	0.24 (0.13, 0.35)	0.005	028 (0.18, 0.38)	0.16 (0.06, 0.27)	0.11 (0.01, 0.22)	0.028
Δ z-score SS	0.60 (0.39, 0.81)	0.42 (0.21, 0.62)	0.38 (0.16, 0.59)	0.145	0.47 (0.27, 0.66)	0.20 (−0.01, 0.41)	0.21 (0.01, 0.42)	0.081
Δ z-score FMI	0.42 (0.30, 0.55)	0.30 (0.18, 0.42)	0.22 (0.09, 0.35)	0.025	0.30 (0.16, 0.44)	0.13 (−0.01, 0.28)	0.21 (0.07, 0.35)	0.346

Values are mean (95% confidence interval (CI)), adjusted for country of origin, physical activity, parental overweight/obesity, parental education, intervention/control study group, individual time interval between baseline and follow-up, pubertal status, and baseline values of the examined variables.
Abbreviations: BMI, body mass index; WC, waist circumference; SS, sum of skinfolds (subscapular + tricipital); FMI, fat mass index.

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Table 3a Changes in anthropometric variables over the 6-year follow-up across tertiles of dairy calcium intake defined at baseline.

	Boys				Girls			
	I (n = 389)	II (n = 428)	III (n = 415)	P for trend	I (n = 426)	II (n = 410)	III (n = 415)	P for trend
Δ z-score BMI	0.36 (0.27, 0.44)	0.33 (0.25, 0.42)	0.21 (0.12, 0.29)	0.016	0.09 (0.01, 0.18)	0.04 (−0.04, 0.13)	0.06 (−0.02, 0.14)	0.570
Δ z-score WC	0.44 (0.33, 0.56)	0.36 (0.25, 0.47)	0.20 (0.09, 0.31)	0.004	0.25 (0.15, 0.35)	0.19 (0.08, 0.29)	0.12 (0.02, 0.22)	0.083
Δ z-score SS	0.52 (0.31, 0.73)	0.58 (0.37, 0.78)	0.30 (0.09, 0.51)	0.143	0.42 (0.21, 0.61)	0.20 (0.01, 0.41)	0.27 (0.07, 0.48)	0.344
Δ z-score FMI	0.37 (0.25, 0.50)	0.39 (0.05, 0.51)	0.18 (0.05, 0.30)	0.030	0.25 (0.11, 0.39)	0.18 (0.04, 0.32)	0.22 (0.08, 0.36)	0.732

Values are mean (95% confidence interval (CI)), adjusted for country of origin, physical activity, parental overweight/obesity, parental education, intervention/control study group, individual time interval between baseline and follow-up, pubertal status, and baseline values of the examined variables.
Abbreviations: BMI, body mass index; WC, waist circumference; SS, sum of skinfolds (subscapular + tricipital); FMI, fat mass index.

found that consumption of yogurt, and higher intakes of dairy, calcium from dairy sources, and vitamin D were all independently associated with lower body fat in children as measured by subscapular skinfold thickness.

The association between calcium intake and body fat parameters in children has been evaluated also longitudinally. In a 5-years longitudinal study, higher levels of calcium intake were associated with lower body fat in 53 pre-school children [18]. A follow-up study by Skinner et al. [19] in the same population confirmed that the inverse relation between calcium intake and percentage body fat persisted at 8 years of age.

Furthermore, Dixon et al. [20] evaluated the association between calcium and dairy intake and obesity in 342 children, aged 4-to 10 years, with normal and elevated plasma cholesterol concentrations. Cross-sectional and longitudinal analyses showed a negative association between calcium intake and dairy and BMI, sum of skinfolds, and trunk fat in non-hypercholesterolemic children aged 7- to 10-years. Conflicting with most evidence, Berkey et al. in a longitudinal analysis on a large adolescent population found that dietary calcium and milk intakes were positively associated with self-reported BMI gain over time [21].

In a 2-years prospective study in a small sample of peripubertal girls, Barr reported at baseline an inverse association between calcium intake and body fat, that disappeared after adjustment for covariates, while calcium intake was not associated with change in fat over the follow-up [22].

Several reasons may contribute to the heterogeneity of the above mentioned results such as different dietary intake assessment methods (e.g., food frequency questionnaires vs 24-h dietary recall), different methods for anthropometric measures (e.g. measured vs reported), adjustment or not for specific confounders in the statistical models, and different demographics of the populations evaluated (e.g. age categories, sex distribution).

Our data showed that lower calcium intake at baseline was associated with an increase in adiposity indices over time only in boys. In girls, we did not find a significant association between calcium intake at baseline and anthropometric variations during the follow−up.

Interestingly, these results are in accordance with those reported by Barr in a small population of Canadian prepubertal girls [22]. However, Moreira et al. found an inverse relationship between calcium intake and BMI only in girls, although in a cross-sectional setting [37]. Although our prospective analysis was adjusted by the pubertal status, a differential role of sex hormones over the pubertal period in the modulation of the effect of dietary calcium on adiposity cannot be excluded. Thus, further studies are needed to explore if there is a sex-related modulation of the association between dietary calcium intake and body mass.

The possible effect of dietary calcium on body weight regulation has been explored by randomized trials of dairy products or calcium supplementation in both adults and children with conflicting results. A complete discussion of the results of the intervention trials is far beyond the scope of this paper. Of note, a recent meta-analysis of the effects of calcium supplementation on body weight suggests a modest but significant negative correlation between calcium supplementation and body weight changes in children and adolescents [11]. However, to further confirm the uncertainty about the role of supplemental calcium as possible modulator of body fat and weight, a recent well-designed randomized trial in adolescent girls did not support the efficacy of this measure to reduce body fat, at least in overweight girls [38].

Several mechanisms have been advocated to explain the relation between calcium intake and adiposity. The first

Table 4 Odds Ratio of incident overweight/obesity over the 6-year follow-up by tertiles of total calcium intake defined at baseline.

	Boys (n = 971)			Girls (n = 986)		
	OR	(95% CI)	P value	OR	(95% CI)	P value
I	2.69	(1.63, 4.45)	<0.0001	1.25	(0.76, 2.05)	0.387
II	1.91	(1.16, 3.12)	0.010	1.31	(0.81, 2.12)	0.273
III	1	—	—	1	—	—

Logistic regression analysis adjusted for country of origin, physical activity, parental overweight/obesity, parental education, intervention/control study group, pubertal status, individual time interval between baseline and follow-up.
Abbreviations: CI = confidence interval; OR = odds ratio.

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Table 4a Odds Ratio of incident overweight/obesity over the 6-year follow-up by tertiles of dairy calcium intake defined at baseline.

	Boys (n = 971)			Girls (n = 986)		
	OR	(95% CI)	*P* value	OR	(95% CI)	*P* value
I	2.32	(1.43, 3.78)	0.001	1.27	(0.79, 2.04)	0.329
II	2.07	(1.28, 3.36)	0.003	1.05	(0.65, 1.69)	0.853
III	1	—	—	1	—	—

Logistic regression analysis adjusted for country of origin, physical activity, parental overweight/obesity, parental education, intervention/control study group, pubertal status, individual time interval between baseline and follow-up.
Abbreviations: CI = confidence interval; OR = odds ratio.

plausible and most popular mechanism was proposed by Zemel and Miller [9]. Using animal models, the authors showed that intracellular calcium levels could influence adipocyte fat metabolism. High dietary calcium intake is associated with reduced 1,25-vitamin D levels which in turn act in decreasing calcium influx into the cell and, thus, the intracellular levels of the ion: these modifications eventually stimulate lipolysis and inhibit lipogenesis in the adipocyte. In contrast, high intracellular calcium levels (low dietary calcium) are associated with increased fat synthesis and reduced lipolysis via calcium-dependent mechanisms. Moreover, dietary calcium intake could influence fat metabolism by increasing fecal fatty acid excretion [39]. The increase in fecal fat loss has been suggested to be caused by either the formation of insoluble calcium soaps or the formation of insoluble conjugates between calcium-phosphate complexes and bile acids [40]. Some evidence shows that dairy sources of calcium are more effective in reducing weight gain than other sources of calcium. This effect is likely attributable to bioactive compounds contained in dairy foods, including the angiotensin-converting enzyme inhibitors and the rich concentration of branched-chain amino acids in whey, which may act synergistically with calcium to reduce body fat accumulation [41].

However, all the proposed mechanisms, although biologically plausible, still lack confirmation in human long-term studies.

Our study has several strengths. First, this is one of the few studies that examined the association between energy-adjusted calcium intake and obesity in European children and adolescents. Our computer-assisted 24-h dietary recall offered the opportunity to evaluate separately calcium intake from dairy and non-dairy foods. Other important strengths of the study are its multicentric nature, the large sample size, and the extended follow-up. We used standardized phenotypic measurements within the eight European countries participating in the survey. All measurements were conducted according to detailed standard operation procedures. In particular, subsamples of study subjects were repeatedly examined to calculate the inter- and intra-observer reliability of anthropometric measurements [28].

Despite the many strengths, there are also limitations. First, the present analysis, based on single 24-HDR, may not reflect habitual dietary intake, relies on memory, and is susceptible to over- and under-reporting. However, the instrument has been validated to estimate 24-h dietary intake [34]. Of note, a single 24-HDR is considered as a valid tool for the estimation of dietary intake at the population level [41]. Although we excluded children reporting the use of calcium supplements during the week before physical examination, the chronic use of calcium or other dietary supplements was not captured by our questionnaire. A limitation of the longitudinal analysis is the lower number of children attending the follow-up examination. However, the longitudinal association of baseline dietary calcium intake with adiposity indices and risk of developing overweight/obesity clearly emerged over the follow-up, notwithstanding the expected reduction of the sample size, mainly due to the burden of the extensive examination protocol in free-living school children.

Finally, dairy foods largely contributed to total calcium intake in our study population. Although calcium has generally being considered the anti-adipogenic component of dairy foods, these contain other macro- and micronutrients that may have effects on appetite and regulation of energy intake. The observational nature of our study does not allow to speculate on the potential mechanisms of the effect of calcium and/or dairy foods on body fat accumulation [42].

In conclusion, our results show an association between dietary calcium intake and measures of obesity in children. When separately examining dietary calcium from dairy and non-dairy sources, the observed effect was attributable exclusively to dairy calcium intake. In detail, at the cross-sectional examination, intake of calcium was inversely associated with the prevalence of overweight/obesity and with anthropometric indices in both boys and girls. After six years of follow-up, we found that higher dietary calcium intake at baseline was associated with reduced body fat accumulation only in boys. Among boys who were normal weight, lower calcium intake at baseline predicts an increased risk of overweight/obesity over the follow-up. No clear association between baseline dietary calcium and measures of obesity was observed in girls after the six years follow-up. Our data confirm that dietary dairy calcium intake may play a role in the modulation of body fat in developmental age. However, the existence of a sex-related difference in the association deserves further investigations.

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Conflicts of interest

The authors declare no competing financial interests.

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The authors' responsibilities were as follows: AS, PR: designed the research; AN, SS: conducted the research; all the authors collected and provided data necessary for research in this multicenter stuy; AN, SS, PR, AS: analyzed data and performed statistical analysis; AN, SS, PR, AS: wrote the paper; LAM critically contributed to its content.; AS, PR: had primary responsibility for final content; All the authors reviewed and edited the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.01.015.

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