



Consumption of soy-based infant formula is not associated with early onset of puberty

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Abstract

Purpose The use of soy products is common in young children with cow milk allergy (CMA). The aim was to examine prospectively the association between infantile consumption of soy-based formula, growth parameters and early pubertal signs, in comparison to cow milk-based formula.

Methods A nested case–control study was conducted, selected from a cohort of infants prospectively followed from birth until the age of 3 years for eating habits and the development of IgE-mediated CMA. Infants who consumed only soy-based formula were included in the soy group. The control group was randomly selected from those without IgE-CMA and not receiving soy formula. Study participants were reevaluated between ages 7.8 and 10.5 years by an interview, nutritional intake by 3 days diaries, and height, weight, and pubertal signs by physical examination.

Results The soy-fed group included 29 participants (17 males), median age 8.92 years IQR (8.21, 9.42). The control group included 60 participants (27 males), median age 8.99 years IQR (8.35, 9.42). The groups had comparable height and BMI z scores (-0.17 ± 1.08 versus -0.16 ± 1.01 , $p=0.96$, and 0.67 ± 1.01 versus 0.53 ± 1.02 , $p=0.56$, for soy and control groups, respectively). Four (three males and one female) from the soy-group (13.8%) and eight females from the control-group (13.3%) had early pubertal signs ($p=0.95$). No association was detected between puberty and infantile nutrition, after controlling for BMI and family data. No association with puberty or differences between groups were found in current daily consumption of soy, micronutrients, energy, carbohydrates, fat, and protein.

Conclusions This is the first prospective, physical examination-based study, demonstrating no association between infantile soy-based formula consumption and growth and puberty parameters.

Keywords Growth · Children · BMI · Prospective · Cow milk allergy · Nutritional intake

Introduction

Soy and soy-based product consumption has become widespread in recent years. It is a major staple in some select populations, such as vegetarians and vegans [1]. Recent data show that 12% of bottle-fed infants in the USA receive soy-based formula [2]. Among infants with IgE-mediated cow's milk allergy, breast-feeding, soy-based formulas, and hypoallergenic formulas (extensively hydrolyzed formulas/ amino acid-based formulas) are the only options [3]. Soy products contain phytoestrogens (isoflavones) that may act as weak hormonal disruptors due to their functional similarity to mammalian estrogens and their active metabolites [4]. Infants who were fed soy-based formulas had significantly higher blood concentrations of isoflavones as compared to breast-fed and milk-based formula-fed babies [5].

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Over the past several decades, the onset of puberty has been occurring at an earlier age [6], which may result in anthropometric [7], psychological [8], and medical consequences [9, 10]. It has been speculated that the consumption of soy-based products in infancy and childhood may contribute to the trend of early puberty [11]. However, data in the literature are inconclusive. It is unclear whether the measured phytoestrogens are biologically active and little is known regarding their clinical hormonal impact during school-age growth and pubertal development [12]. Furthermore, methodological differences among studies limit the ability to reach meaningful conclusions regarding this question [13–20].

The aim of this study was to assess the association between infantile consumption of soy-based formula and the timing of secondary sexual characteristics in a prospective manner, utilizing data regarding infantile feeding and assessment of growth and puberty by physical examination, and considering confounding factors such as current nutritional and behavioral habits, and familial trends.

Subjects and methods

Study design

This was a nested case–control study, based on a prospectively followed cohort of participants, born 2004–2006, and followed from birth for eating habits during infancy. Those selected for the present study were approached again during 2012–2016 for additional clinical data. Demographic and clinical data were collected by a pediatrician, 3-day food diaries were reviewed by a registered dietician, and a physical examination including growth and pubertal assessment was performed by a board-certified pediatric endocrinologist, who was blinded to exposures. The study was approved by the Institutional Ethics Committee of Assaf Harofeh Medical Center and conducted according to the principles of the Declaration of Helsinki on biomedical research involving human patients. Informed consent was obtained prior to enrollment.

Study population

The study cohort was selected from a prospectively followed infant population born at a single medical center (Assaf Harofeh Medical Center, Zerifin, Israel). Newborns born during 2004–2006 were followed for the development of milk allergy during the first 6 months of life by telephone calls, and for milk formula intake until age 3 years [21]. Sixty-six (0.5%) developed an IgE-mediated cow milk allergy (IgE-CMA), 71 developed non-IgE-mediated milk intolerance, and 12,638 were defined healthy, since no gastrointestinal symptoms associated with food were reported

during the follow-up [21]. The experimental group termed “soy group” consisted of infants pooled from those with IgE-mediated CMA, who ingested soy-based formula for longer than 3 months, usually at the end of breast-feeding or in combination with breast-feeding. The control group comprised children who were randomly selected from the population defined healthy. The computer selected 235 children, to include at least a rate of 2:1 between the study groups. Inclusion criteria for both groups included: data available regarding nutritional habits during at least the first 6 months of life and agreement for pubertal physical examination. Exclusion criteria included: refusal for pubertal physical examination, consumption of only breast milk during first 6 months of life, and consumption of soy-based formula in the control group. The soy group included 29 children. This constituted 43.9% (29/66) of the initial cohort categorized as IgE-CMA. Of the remaining children from the original IgE-CMA cohort, 5 were lost to follow-up, 5 never consumed soy-based formula, and 27 refused physical examination. Sixty control participants, who were randomly selected from the large healthy cohort, answered our calls and were compatible with the inclusion and exclusion criteria.

Demographic and clinical data collection

Data collected in this study included retrieval of data from the initial infantile database, including: birth weight, birth week, ethnicity, infantile food habits, and maternal age. Data collected at the school age assessment included family history including obesity, early or delayed puberty, age of maternal menarche and age of paternal shaving, parental height, child’s physical activity levels and nutritional habits, illnesses, and current medications. Height was measured to the nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 0.1 kg (Tanita WB-3000). Body mass index (BMI) and *z* scores were calculated according to the Centers for Disease Control and Prevention growth charts [22].

Tanner score was used to characterize sexual maturation. The pre-pubertal state (Tanner 1) was defined as testicular volume ≤ 3 ml in boys and absence of breast development in girls [23, 24]. Precocious puberty was defined as Tanner stage 2 (T2) before the age of 8 years in females and 9 years in males. Early puberty was defined as T2 at the age of 8–8.5 years in females and 9–9.5 years in males. Premature adrenarche was defined as the sole presence of pubic or axillary hair and odor, at the ages 6–8 years in females and 7–9 years in males, respectively.

Dietary intake analysis

All participants provided a detailed 3-day food diary (two typical weekdays and 1 day during the weekend) with the aid

of their parents, under the guidance of the study dietician. Nutrient values of the food records were determined using a computerized program (Tzameret) based on local food tables developed by the Israeli Ministry of Health [25]. Results of nutrient intake were reported as absolute values and also as a percentage of the dietary reference intakes (DRI) for energy, carbohydrates, proteins, and several micronutrients [26]. Macronutrient intake was also reported as percentage of energy intake [26]. Soy food consumption was measured in servings, which by definition contained approximately 6 g of soy protein per serving.

Outcome measures

The primary outcome measure was pubertal state and the secondary outcome measures were weight and BMI.

Secondary outcome measures included height and BMI z scores, controlled for group, family history, and nutritional intake.

Statistical analysis

Data were stored on a spreadsheet and analyzed on SPSS v21 (IBM Inc. USA). Continuous variables that were normally distributed are presented as mean $\pm$ SD, and those with a non-normal distribution are presented as median and interquartile range (IQR). Categorical variables were assessed using frequency tables and are presented as n (%). Continuous variables were compared between groups, using independent sample t test or Mann–Whitney test. Categorical variables were compared using Chi square

test or Fisher exact test. Analysis was controlled for confounding factors, including family history of precocious and delayed puberty, BMI, daily soy intake, and breast-feeding. Analysis included Levene's test for equality of variances and Pearson correlations. Cases with missing data were excluded. Cases with only dietary data missing were not excluded from analysis. The final study population included in the analysis enabled a power of 50% and two-sided tests with results considered significant at $p < 0.05$.

Results

Demographic data

The study population included 89 children (44 males) from the original 2004–2006 cohort. The soy group consisted of 29 participants, median age 8.92 years IQR (8.21, 9.42), of whom 17 were males (59%). The healthy control group included 60 participants, median age 8.99 years IQR (8.35, 9.42), of whom 27 were males (45%). There were no significant difference between the groups in their age, gender distribution, maternal characteristics, weight for gestational age, family history, and behavioral habits. There was a significantly longer duration of breast-feeding in the soy group compared with control group: 7.98 months IQR (4.48, 13.35) compared with 1.08 months IQR (0, 5.33), $p < 0.001$ (Table 1).

Table 1 Demographic and clinical characteristics of study population according to groups

Characteristics	Soy group $N=29$	Control group $N=60$	p value
Gender (F:M)	12:17	33:27	0.23
Age (years) ^b	8.92 (8.21, 9.42)	8.99 (8.35, 9.42)	0.85
Gestational age (weeks) ^b	39 (38, 40)	39 (37.2, 40)	0.39
Birth weight (g) ^a	3269 $\pm$ 337	3072 $\pm$ 676	0.15
Age of mother at birth (years) ^a	29.17 $\pm$ 4.6	30.63 $\pm$ 5.5	0.25
Breastfeeding length (months) ^b	7.98 (4.48, 13.35)	1.08 (0, 5.33)	<0.001
Soy exposure (months) ^b	23.7 (12, 44.5)	0	Inclusion criteria
Mean MPH Z Score (SDS) ^a	0.29 $\pm$ 0.84	0.1 $\pm$ 0.85	0.34
Maternal and/or paternal early puberty (%)	5 (17.9%)	12 (20.3%)	0.77
Familial obesity (%)	14 (48%)	26 (43%)	0.52
Height z score (SDS) ^a	-0.17 $\pm$ 1.08	-0.16 $\pm$ 1.01	0.96
BMI z score (SDS) ^a	0.67 $\pm$ 1.01	0.53 $\pm$ 1.02	0.56
Overweight/obesity (%)	6 (20.7%)	12 (20.0%)	0.94
Physical activity ($\leq$ 3 sessions/week)	89.65%	85%	0.34
Sweet beverages ($>$ 4 cups/week)	27.59%	21.67%	0.90

MPH midparental height

^aMean and standard deviation

^bMedian and IQR

Growth and puberty data

No significant differences were found between the groups in height z scores (0.17 ± 1.08 , versus 0.16 ± 1.01 , $p = 0.96$) and BMI z scores (0.67 ± 1.01 versus 0.53 ± 1.02 , $p = 0.56$), for soy and control groups, respectively (Table 1). There were a total of four children in the soy group (13.8%) and eight children in the control group (13.3%) who had signs of premature adrenarche, precocious puberty, or early puberty, $p = 0.95$. Specifically, one female and two males from the soy group and six females from the control group had signs of precocious or early puberty ($p = 0.96$). One male from the soy group and two females from the control group had signs of premature adrenarche ($p = 0.98$) (Table 2).

Nutritional data

Eighty-four food diaries were completed, 26 from the soy group (89.7%) and 58 from the control group (96.7%). No significant differences were observed in the energy, carbohydrate, fat, protein, and micronutrient consumption between the groups. All children had an overall balanced diet based on the percent of macronutrients from total energy. However, the consumption of several micronutrients (vitamin A, vitamin E, calcium, potassium) did not meet the DRI recommendations (mean intakes $< 70\%$ DRI). No significant differences were found between groups (Table 3).

Milk allergy was resolved by the age of 3 years in 23/29 of the children in the soy group. In both groups, the total amount of soy was of very low proportion of their total daily intake (Table 3), although its consumption was higher in the soy group compared with the control group (0.29 ± 0.78

Table 2 Incidence of precocious, early, and premature adrenarche according to study groups

Characteristics	Soy group		Control group		<i>p</i> value
	<i>N</i> = 29 [<i>n</i> (%)]	F:M	<i>N</i> = 60 [<i>n</i> (%)]	F:M	
Precocious puberty	1 (3.4)	1:0	4 (6.7)	4:0	0.54
Early puberty	2 (6.9)	0:2	2 (3.3)	2:0	0.45
Premature adrenarche	1 (3.8)	0:1	2 (3.3)	2:0	0.98
Total	4 (13.8)	1:3	8 (13.3)	8:0	0.95

Precocious puberty was defined as T2 before the age of 8 years in females and 9 years in males

Premature adrenarche was defined as the sole presence of pubic or axillary hair and odor at the ages 6–8 years in females and 7–9 years in males

Early puberty was defined as T2 at the age of 8–8.5 years in females and 9–9.5 years in males

Table 3 Daily nutritional analysis of 3 days food diaries, according to study groups

Nutrient	Soy group <i>n</i> = 26	Control group <i>n</i> = 58	<i>p</i> value
Energy (kcal) ^a	1551.1 $\pm$ 359.0	1424.7 $\pm$ 320.6	0.11
Energy (%DRI) ^b	87.3 (69.1, 102.8)	91.6 (73.2, 110.1)	0.63
Protein (g) ^a	60.4 $\pm$ 13.0	58.2 $\pm$ 14.3	0.50
Protein (% of energy) ^b	16.0 (14.2, 17.6)	16.7 (14.4, 19.4)	0.27
Fat (g) ^b	50.5 (45.6, 63.3)	50.4 (40.8, 60.3)	0.50
Fat (% of energy) ^a	31.8 $\pm$ 6.3	32.1 $\pm$ 4.5	0.80
Carbohydrates (g) ^b	190.7 (154.0, 254.1)	163.8 (136.3, 215.6)	0.14
Carbohydrates (% of energy) ^a	50.1 $\pm$ 7.4	49.5 $\pm$ 6.1	0.68
Iron (%DRI) ^b	117.3 (94.8, 156.9)	101.3 (76.3, 113.7)	0.16
Zinc (%DRI) ^b	84.7 (70.5, 108.3)	87.3 (63.7, 107.4)	0.81
Calcium (%DRI) ^b	26.6 (16.5, 44.9)	34.1 (27.6, 44.4)	0.07
Phosphorus (%DRI) ^b	68.7 (54.2, 97.1)	74.8 (58.6, 97.0)	0.39
Vitamin A (%DRI) ^b	45.1 (27.8, 73.0)	71.8 (39.8, 85.8)	0.09
Vitamin E (%DRI) ^b	53.6 (40.0, 64.4)	42.8 (30.1, 61.2)	0.15
Soy products (no. servings/day)	0.3 $\pm$ 0.8	0.1 $\pm$ 0.2	0.06

Data are presented as percent of energy or DRI, calculated according to gender and age

^aMean and standard deviation

^bMedian and IQR

soy servings/day versus 0.05 ± 0.24 soy servings/day, respectively, $p = 0.056$).

Risk factors for puberty analysis

On propensity analysis of puberty according to group, no parameter was found to differ significantly between groups or be associated with early pubertal signs. Analysis included gender ($p = 0.07$), parental puberty ($p = 0.18$), family obesity ($p = 0.70$), BMI ($p = 0.11$), breast-feeding length ($p = 0.52$), and soy product consumption ($p = 1$).

Data analysis of all those who had any early signs of puberty from both groups as a whole ($n = 12$), compared with those who had no pubertal signs (pre-pubertal) ($n = 77$), demonstrated that those with earlier signs of puberty had higher growth parameters: BMI z score 1.20 ± 1.13 versus 0.48 ± 0.98 , $p = 0.022$ and height z score 0.64 ± 0.87 versus -0.29 ± 1 , $p = 0.003$, respectively. In addition, those who had early signs of puberty reported of less weekly physical activity compared to those with no pubertal signs, and 10 versus 15% of patients reported of physical activity more than 3 times per week, $p = 0.032$. On logistic regression analysis of parameters contributing to puberty, being in the soy group was not found to be a significant contributor.

Discussion

This is the first prospective study including both real-time infantile data regarding feeding habits and birth parameters, in conjunction with a physical examination at the age of early pubertal onset, demonstrating that infantile soy consumption is not associated with early onset of secondary pubertal signs. Nutritional, behavioral, and familial confounding parameters were accounted for in the analysis.

The percentage of premature adrenarche, precocious puberty, and early puberty in the study population (13.5%) for both “control” and “soy” groups did not differ from that reported from large population databases from the past decade [27]. Signs of early puberty were more common in female participants compared to males, in agreement with the literature that early puberty is far less prevalent among boys than girls in the general population [28].

Results from several previous studies are consistent with the findings noted here [11, 13–16]. Strom et al. [11], in a large retrospective cohort study, reported no differences in pubertal parameters between infants fed soy versus those fed cow milk-based formula. However, their pubertal data were derived from a structured telephone interview and may have been subject to recall bias and to misdiagnosis. No association was found between soy intake and early onset of menarche in a cross-sectional, Web-based American study [13]. Furthermore, Cheng et al. [14] reported that German

girls with higher prepubertal isoflavone intakes entered puberty at the higher ages within the normal range.

Our results support the findings provided by Andres et al. [16], who demonstrated no statistically significant differences in ultrasonographic measures of breast bud, uterus, ovaries, prostate and testes, in a group of 100 pre-pubertal children, at 5 years of age, who were followed prospectively, with a third of them consuming soy-based formula during infancy. However, our data add the clinically relevant information of no difference between those ingesting soy formulae versus those on a non-soy formula-based feeding regimen, based on physical examination and face-to-face interview.

On the other hand, there are reports of a positive association between soy formula exposure and sexual development. Infantile physiologic telarche has been associated with soy feeding [17, 18], but there is little indication that this leads to premature puberty. In a case–control study, Kim et al. [19] reported that higher serum isoflavone concentrations were measured in Korean girls diagnosed with precocious puberty; however, their source was not obligatorily from food intake. Adgent et al. [20] reported a trend toward increased risk of early menarche in girls fed soy products in early infancy; however, the reported age is well within the normal age range for menarche (12.4 years).

Numerous factors are thought to impact the timing of the onset of puberty which may confound data analyses. This includes association with family history of early puberty [29], prenatal growth [30] obesity [31], breastfeeding [32], nutritional intake habits [33], physical activity [34], and current soy consumption [17, 18]. These potential confounders were all accounted for in the data acquisition phase and statistical analysis of this study. Current dietary intake data were collected using the recommended methodology for accurate and precise nutritional evaluation [35]. Nutrient intake including consumption of soy-based foods was similar in the soy-based and control groups, and was consistent with national food consumption data [36]. Furthermore, none of the six participants who retained their allergic status and consumed soy-based products instead of cow’s milk-based products throughout childhood had signs of early puberty.

In addition to pubertal stage, we analyzed growth parameters and our results were in agreement with numerous reports and a recent meta-analysis that measured growth parameters during the first 3 years of life [37]. These studies indicate that consumption of soy formula at an early age had little or no impact on anthropometric parameters [37]. Our study is novel in that it reports data for older, school-aged children, a relatively longer follow-up, supporting no significant difference. The differences detected in BMI z score and height z score between pubertal and non-pubertal participants, from both groups are not surprising, or novel, since puberty and body composition are interrelated physiologically [6, 7].

Our study has several strengths. First, the collection of data was carried out in a prospective manner, which eliminated recall bias of the infantile period. Second, pubertal and anthropometric parameters were based on physical examination by a pediatric endocrinologist, providing data not subject to self-assessment or self-recall bias. Third, the addition of 3-day dietary records, which is considered the gold standard for nutritional intake assessment [35], adds to the elimination of other nutritional confounding factors from puberty. The main limitation of the study is its relatively small sample size. However, it was homogenous, without recall bias, and similar in size to the only previously reported prospective study [16]. Nevertheless, our data demonstrate the need for a larger prospective multi-center study based on physical examination, to understand if soy-based infant formula is really an endocrine disruptor, as previously suggested.

In summary, this nested case–control study of a prospectively followed cohort, including a current physical examination and dietary analysis validates previous reports indicating no difference in pubertal development, growth, and BMI *z* scores, among those provided soy-based formula during infancy. This provides important information for physicians and caretakers alike, supporting the safety of soy-based formula consumption during infancy regarding pubertal onset timing.

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Compliance with ethical standards

Conflict of interest There are no reported conflicts of interest for any of the authors.

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References

- Messina M, Messina V (2010) The role of soy in vegetarian diets. *Nutrients* 2:855–888. <https://doi.org/10.3390/nu2080855>
- Rossen LM, Simon AE, Herrick KA (2016) Types of infant formulas consumed in the United States. *Clin Pediatr (Phila)* 55:278–285. <https://doi.org/10.1177/0009922815591881>
- Vandenplas Y, De Greef E, Devreker T (2014) Treatment of cow's milk protein allergy. *Pediatr Gastroenterol Hepatol Nutr* 17:1–5. <https://doi.org/10.5223/pghn.2014.17.1.1>
- Patisaul HB, Jefferson W (2010) The pros and cons of phytoestrogens. *Front Neuroendocrinol* 31:400–419. <https://doi.org/10.1016/j.yfrne.2010.03.003>
- Setchell KD, Zimmer-Nechemias L, Cai J, Heubi JE (1997) Exposure of infants to phyto-oestrogens from soy-based infant formula. *Lancet* 350:23–27. [https://doi.org/10.1016/S0140-6736\(96\)09480-9](https://doi.org/10.1016/S0140-6736(96)09480-9)
- Biro FM, Greenspan LC, Galvez MP (2012) Puberty in girls of the 21st century. *J Pediatr Adolesc Gynecol* 25:289–294. <https://doi.org/10.1016/j.jpag.2012.05.009>
- Carel JC, Lahlou N, Roger M, Chaussain JL (2004) Precocious puberty and statural growth. *Hum Reprod Update* 10:135–147. <https://doi.org/10.1093/humupd/dmh012>
- Downing J, Bellis MA (2009) Early pubertal onset and its relationship with sexual risk taking, substance use and anti-social behaviour: a preliminary cross-sectional study. *BMC Public Health* 9:446. <https://doi.org/10.1186/1471-2458-9-446>
- Prentice P, Viner R (2013) Pubertal timing and adult obesity and cardiometabolic risk in women and men: a systematic review and meta-analysis. *Int J Obes (Lond)* 37:1036–1043. <https://doi.org/10.1038/ijo.2012.177>
- Collaborative Group on Hormonal Factors in Breast Cancer (2012) Menarche, menopause, and breast cancer risk: individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. *Lancet Oncol* 13:1141–1151. [https://doi.org/10.1016/S1470-2045\(12\)70425-4](https://doi.org/10.1016/S1470-2045(12)70425-4)
- Strom BL, Schinnar R, Ziegler EE et al (2001) Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. *JAMA* 286:807–814
- Cao Y, Calafat AM, Doerge DR et al (2009) Isoflavones in urine, saliva and blood of infants: data from a pilot study on the estrogenic activity of soy formula. *J Expo Sci Environ Epidemiol* 19:223–234. <https://doi.org/10.1038/jes.2008.44>
- Segovia-Siapco G, Pribis P, Messina M, Oda K, Sabaté J (2014) Is soy intake related to age at onset of menarche? A cross-sectional study among adolescents with a wide range of soy food consumption. *Nutr J* 13:54. <https://doi.org/10.1186/1475-2891-13-54>
- Cheng G, Remer T, Prinz-Langenohl R, Blaszkewicz M, Degen GH, Buyken AE (2010) Relation of isoflavones and fiber intake in childhood to the timing of puberty. *Am J Clin Nutr* 92:556–564. <https://doi.org/10.3945/ajcn.2010.29394>
- Giampietro PG, Bruno G, Furcolo G et al (2004) Soy protein formulas in children: no hormonal effects in long-term feeding. *J Pediatr Endocrinol Metab* 17:191–196
- Andres A, Moore MB, Linam LE, Casey PH, Cleves MA, Badger TM (2015) Compared with feeding infants breast milk or cow-milk formula, soy formula feeding does not affect subsequent reproductive organ size at 5 years of age. *J Nutr* 145:871–875. <https://doi.org/10.3945/jn.114.206201>
- Freni-Titulaer LW, Cordero JF, Haddock L, Lebrón G, Martínez R, Mills JL (1986) Premature thelarche in Puerto Rico. A search for environmental factors. *Am J Dis Child* 140:1263–1267
- Zung A, Glaser T, Kerem Z, Zadik Z (2008) Breast development in the first 2 years of life: an association with soy-based infant formulas. *J Pediatr Gastroenterol Nutr* 46:191–195. <https://doi.org/10.1097/MPG.0b013e318159e6ae>
- Kim J, Kim S, Huh K, Kim Y, Joung H, Park M (2011) High serum isoflavone concentrations are associated with the risk of precocious puberty in Korean girls. *Clin Endocrinol (Oxf)* 75:831–835. <https://doi.org/10.1111/j.1365-2265.2011.04127.x>
- Adgent MA, Daniels JL, Rogan WJ et al (2012) Early-life soy exposure and age at menarche. *Paediatr Perinat Epidemiol* 26:163–175. <https://doi.org/10.1111/j.1365-3016.2011.01244.x>
- Katz Y, Rajuan N, Goldberg MR et al (2010) Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. *J Allergy Clin Immunol* 126:77–82. <https://doi.org/10.1016/j.jaci.2010.04.020>
- Kuczmarski RJ, Ogden CL, Grummer-Strawn LM et al (2000) CDC growth charts: United States. *Adv Data* 314:1–27

23. Marshall WA, Tanner JM (1969) Variations in pattern of pubertal changes in girls. *Arch Dis Child* 44:291–303
24. Marshall WA, Tanner JM (1970) Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 45:13–23
25. Tzameret [computer program] (2010) Version 2. Jerusalem: Israeli Ministry of Health
26. National Agricultural Library, United States Department of Agriculture United States: Food and Nutrition Information Center. DRI tables and application reports; Available at: http://www.nal.usda.gov/sites/default/files/fnic_uploads/recommended_intakes_individuals.pdf. Accessed 22 Nov 2017
27. Biro FM, Galvez MP, Greenspan LC et al (2010) Pubertal assessment method and baseline characteristics in a mixed longitudinal study of girls. *Pediatrics* 126:e583–e590. <https://doi.org/10.1542/peds.2009-3079>
28. Garibaldi L, Chemaitilly W (2015) Disorders of pubertal development. In: Kliegman RM, Stanton BF, Schor NF, Behrman RE, eds. *Nelson textbook of pediatrics* St. Geme JW, 20th edn. Elsevier, Philadelphia, pp 2656–2662
29. Wohlfahrt-Veje C, Mouritsen A, Hagen CP et al (2016) Pubertal onset in boys and girls is influenced by pubertal timing of both parents. *J Clin Endocrinol Metab* 101:2667–2674. <https://doi.org/10.1210/jc.2016-1073>
30. Sloboda DM, Hart R, Doherty DA, Pennell CE, Hickey M (2007) Age at menarche: influences of prenatal and postnatal growth. *J Clin Endocrinol Metab* 92:46–50. <https://doi.org/10.1210/jc.2006-1378>
31. Kaplowitz PB (2008) Link between body fat and the timing of puberty. *Pediatrics* 121:S208–S217. <https://doi.org/10.1542/peds.2007-1813F>
32. Kale A, Deardorff J, Lahiff M et al (2015) Breastfeeding versus formula-feeding and girls' pubertal development. *Matern Child Health J* 19:519–27. <https://doi.org/10.1007/s10995-014-1533-9>
33. Villamor E, Jansen EC (2016) Nutritional determinants of the timing of puberty. *Annu Rev Public Health* 37:33–46. <https://doi.org/10.1146/annurev-publhealth-031914-122606>
34. Bacil EDA, Mazzardo O, Rech CR, Legnani RF, dos de Campos SW (2015) Physical activity and biological maturation: a systematic review. *Revista Paulista de Pediatria* 33:114–121. <https://doi.org/10.1016/j.rpped.2014.11.003>
35. Baranowski T (2013) 24-h recall and diet record methods. In: Willett W (ed) *Nutritional epidemiology*, 3rd edn. Oxford University Press, New York, pp 49–69
36. Ministry of Health. Mabat Youth- First Israeli National Health and Nutrition Survey. Available at: https://www.health.gov.il/PublicationsFiles/Mabat_2003-2004-b.pdf. Accessed 22 Nov 2017
37. Vandenplas Y, Castrellon PG, Rivas R et al (2014) Safety of soya-based infant formulas in children. *Br J Nutr* 111:1340–1360. <https://doi.org/10.1017/S0007114513003942>