Nutritional issues in Pubertal Timing and Development: A Narrative Review

Considerações Nutricionais no Período da Puberdade e do Desenvolvimento: Uma Revisão Narrativa

Catarina Rocha Leite

ORIENTADO POR: Prof.ª Doutora Maria Raquel Soares de Carvalho Roriz

REVISÃO TEMÁTICA
1.º CICLO EM CIÊNCIAS DA NUTRIÇÃO | UNIDADE CURRICULAR ESTÁGIO
FACULDADE DE CIÊNCIAS DA NUTRIÇÃO E ALIMENTAÇÃO DA UNIVERSIDADE DO PORTO

TC

PORTO, 2025

Resumo

A puberdade assinala o início do desenvolvimento dos caracteres sexuais secundários e da capacidade reprodutiva. O desenvolvimento pubertário envolve uma complexa interação entre fatores neuro-endócrinos e ambientais. Neste sentido, a reativação do eixo hipotálamo-hipófise-gónadas e a subsequente secreção da hormona libertadora de gonadotrofina são componentes fundamentais deste processo. Nos últimos anos, tem aumentado a prevalência da puberdade precoce, acarretando uma série de problemas de saúde associados. Ainda que os mecanismos exatos responsáveis pela puberdade precoce permaneçam desconhecidos, o estado nutricional emerge como um fator modificável de grande relevância. Esta revisão narrativa tem como objetivo reunir evidências sobre a complexa associação entre a nutrição e o período da puberdade e do desenvolvimento. Relativamente à amamentação, apesar da existência de resultados divergentes, esta parece exercer um efeito protetor sobre o desenvolvimento pubertário prematuro, ao contrário das fórmulas infantis. Adicionalmente, parece verificar-se uma associação entre a ingestão energética total e o índice de massa corporal com a puberdade precoce, sendo que uma ingestão energética superior e um índice de massa corporal elevado contribuem para a mesma. Em relação à ingestão de macronutrientes, a proteína é o único que apresenta uma relação mais evidente entre a sua sobreingestão e a puberdade precoce, não tendo os hidratos de carbono e a gordura o mesmo nível de evidência. No caso do papel dos micronutrientes, a evidência encontrada na literatura é limitada e os mecanismos envolvidos não se encontram ainda devidamente descritos. Serão necessários estudos adicionais sobre o papel da

nutrição no desenvolvimento pubertário precoce, de modo a travar o aumento da sua prevalência.

Palavras-Chave: puberdade precoce; maturação sexual; crescimento e desenvolvimento; nutrição; dieta

Abstract

Puberty marks the beginning of the development of secondary sexual characteristics and reproductive capacity. Pubertal development involves a complex interaction between neuro-endocrine and environmental factors. In this sense, the reactivation of the hypothalamic-pituitary-gonadal (HPG) axis and the subsequent secretion of gonadotrophin-releasing hormone (GnRH) are fundamental components of this process. In recent years, the prevalence of precocious puberty (PP) has increased, leading to a series of associated health problems. Although the exact mechanisms responsible for PP remain unknown, nutritional status has emerged as a modifiable factor of great relevance. This narrative review aims to gather evidence on the complex association between nutrition and the period of puberty and development. Regarding breastfeeding, despite divergent results, it seems to have a protective effect on premature pubertal development, unlike infant formula. In addition, there seems to be an association between total energy intake (TEI) and body mass index (BMI) and PP, with higher TEI and higher BMI contributing to it. As far as macronutrient intake is concerned, protein is the only one that shows a clearer link between its overconsumption and PP, while carbohydrates and fat do not have the same level of evidence. When it comes to the role of micronutrients, the evidence found in the literature is limited and the mechanisms involved have not yet been properly described. Further studies on the role of nutrition in precocious pubertal development will be necessary in order to stop the increase in its prevalence.

Keywords: precocious puberty; sexual maturation; growth and development; nutrition; diet

List of abbreviations

APHV – Age at peak height velocity

ATO – Age at take-off

BMI – Body mass index

CPP – Central precocious puberty

FSH – Follicle-stimulating hormone

GABA - Gamma aminobutyric acid

GnRH – Gonadotrophin-releasing hormone

HPG – Hypothalamic-pituitary-gonadal

IGF-1 - Insulin-like growth factor I

LH – Luteinizing hormone

MUFA - Monounsaturated fatty acid

PHV – Peak height velocity

PP – Precocious puberty

PPP – Peripheral precocious puberty

PUFA – Polyunsaturated fatty acids

TEI - Total energy intake

TS – Tanner Scale

WHO – World Health Organization

Table of contents

Introduction

Puberty is characterized as a period of various physical, emotional and physiological changes that can last 2 to 3 years. It is marked by the beginning of the development of secondary sexual characteristics and the acquisition of the capacity for sexual reproduction.[1-4] The timing of puberty results from the interaction between endogenous (such as neuroendocrine and genetic aspects) and exogenous factors (like general health, physical exercise, nutrition and environmental factors). It involves the activation of the HPG axis with a consequent secretion of sexual hormones, which are responsible for the appearance of secondary sexual characteristics.[2, 5]

To monitor progress in pubertal development, the Tanner Scale (TS) can be used. This tool describes 5 stages of physical development for the following sexual characteristics: pubic hair growth (applied to both sexes), breast development (for girls) and genital development (for boys). The onset of puberty corresponds to stage 2 of the TS, but it has different meanings for each. In girls, this stage is characterised by the development of a palpable breast bud under the areola (B2), which can also be called thelarche. In boys, this stage, also called gonadarche, represents a testicular volume equal to or greater than 4ml (G2).[2, 6, 7] All the stages of the TS described in detail can be found in Tables 1, 2 and 3, Appendix B.

Other markers can be used to assess pubertal development. Age at take-off (ATO) marks the beginning of the pubertal growth spurt, being the age at which the lowest height velocity occurred before its subsequent continuous acceleration. In girls, ATO occurs between the ages of 9 and 10, while in boys it's

between the ages of 10 and 12.[8] This continuous acceleration in height will culminate in peak height velocity (PHV), the moment when height gain is maximum, reflecting the apex of somatic growth acceleration.[8, 9] In the specific case of boys, voice breaking is characterised as a change in the pitch and sonority of the voice and is a late event in male puberty.[10, 11] In turn, the onset of menarche is a late event in female puberty, occurring after the onset of breast development and growth spurt.[12]

In the last few decades, the timing of puberty has become earlier[2, 4, 13] with its onset occurring 12 to 18 months earlier.[2] This data makes PP a worldwide problem. Several studies have shown an association between PP and numerous health problems, such as type 2 diabetes[14-16], obesity[17-19], breast cancer[1, 20], testicular cancer[21], heart diseases[16] and psychological problems[22]. The exact mechanism for the occurrence of an earlier onset of puberty is still unknown, however the contribution of modifiable factors in this process seems to be relevant, being nutrition one of the most important examples. [2, 4, 5] In fact, 25% of the variation in the timing of puberty can be explained by nutritional status.[23] For this reason, it is necessary to understand the nutritional mechanisms that act on pubertal development so that, in the future, recommendations can be developed to reduce the incidence of PP.

This narrative review aimed to gather evidence on the complex association between nutrition and pubertal timing and development.

Methods

To conduct this narrative review, a search for scientific evidence was carried out in the *PubMed* and *Scopus* databases between March and May 2025. The keywords used were the following (alone or combined with the Boolean operands

'AND' or 'OR'): "precocious puberty", "puberty timing", "puberty onset", "pubertal development", "peak height velocity", "age at peak height velocity", "age at take-off", "menarche", "age at menarche", "voice breaking", "growth spurt", "pubarche", "hormones", "BMI", "obesity", "overweight", "nutrition", "diet", "micronutrients", "macronutrients", "breastfeeding", "formula feeding". Articles published in English - including clinical trials, longitudinal studies, meta-analyses, case-control studies, systematic and narrative reviews - conducted in healthy humans were included, with no time restrictions applied. The bibliographic references of the articles found and selected in the above-mentioned search were also consulted. At last, bibliographic references were organised using the software EndNoteX21®.

1. What do we know about puberty?

1.1. Physiology of Puberty

Physiological puberty begins between the ages of 8 and 13 for girls, or between 9 and 14 for boys.[2, 5] This period is related to the reactivation of the HPG axis, which is also responsible for the phenomenon of "mini-puberty", that occurs in the first 6 months of life. After birth, there is a decrease in the maternal steroid hormones responsible for suppressing HPG axis, which causes an increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones lead to the secretion of testosterone in boys and estradiol in girls. It is this period of "mini puberty" that, in the first few months of life, influences the development of the genitals and cognitive development, as well as fertility, growth and body composition. During the following years, the HPG axis remains inactive until the

onset of puberty when it is disinhibited, and the pulsatile secretion of GnRH is re-initiated. In turn, this hormone stimulates the release of LH and FSH, which induce the production of the sex hormones responsible for the development of secondary sexual characteristics.[5, 23] (Figure 1, Appendix A)

GnRH secretion is regulated by inhibitory and excitatory control mechanisms. Gamma aminobutyric acid (GABA) is the main neurotransmitter responsible for inhibitory control, while kisspeptin, neurokinin B, glutamate, endorphins, neuropeptide Y, opioids, melatonin and leptin are stimuli responsible for activating GnRH secretion.[2, 5, 23] Kisspeptin and leptin in particular, seems to play an important role in the phenomenon of PP.

Kisspeptin and its receptor, as well as neurokinin B and its receptor, act to regulate GnRH secretion.[2, 5, 23, 24] Their stimulatory effect increases during puberty, when the inhibitory effect of dynorphin and its receptor on GnRH secretion is blocked. It is also known that the inactivation of kisspeptin gene may result in the absence of pubertal development.[2] In addition, the administration of this protein stimulates the release of GnRH in prepubertal and pubertal mammals.[24] Kisspeptin is also influenced by premature malnutrition.[2, 5, 23]

On the other hand, leptin acts not only to regulate appetite and energy expenditure, but also to control the HPG axis. Its role in fertility has already been explored in rodents, with the acceleration of the onset of reproductive function following the administration of this hormone. Furthermore, cases have been reported where there was no progression through puberty in people who carried mutations in the leptin gene and its receptor.[25] It is also known that the concentration of this hormone increases before the onset of puberty and it is also affected by early life nutrition.[5]

Scientific evidence had already pointed to a possible association between leptin and kisspeptin, with the first being a positive regulator of the second. However, this association has not yet been fully studied and, moreover, the whole system surrounding the timing of puberty is quite complex.[5, 23]

1.2. Precocious Puberty

PP is defined as the appearance of the secondary sexual characteristics, referring to stage B2 and G2 of TS, before the age of 8 or 9 in girls and boys, respectively, if the progression of pubertal development occurs immediately.[23] It can be divided into two types: central precocious puberty (CPP) and peripheral precocious puberty (PPP).[23]

Early maturation of the HPG axis is the cause of CPP, and this early maturation can occur due to neurological problems or have an idiopathic origin, being associated with a genetic, metabolic or environmental component.[2, 23, 26] This form of PP is more common in female children.[2] In the case of PPP, there is a peripheral production of sex hormones, which is independent of gonadotrophin. The hormones are produced by the gonads or adrenal glands, or when there is exposure to exogenous sources of hormones.[2, 23, 26]

The diagnosis of PP requires knowledge of the child and family history, as well as physical, hormonal and radiological exams.[23]

2. Infant´s nutrition and its influence on puberty

2.1. Breastfeeding

Breast milk is the best food for newborns, and it also has benefits for the immune system and neurological development of children.[5] According to the

World Health Organization (WHO), breastfeeding should be the exclusive feeding process until at least 6 months of age, when complementary feeding should be introduced.[27]

In a prospective cohort study carried out in Northern California, the authors used TS to assess pubertal development in a total of 3331 mother-daughter pairs. It was found that girls who were not breastfed were more likely to have earlier development of the breast (thelarche) and pubic hair, compared to girls who were breastfed for 6 months or more.[28] Also, Al-Sahab et al. showed that a 1 month increase in exclusive breastfeeding reduced the risk of premature menarche by 6%.[29] Applying the same main outcome, a retrospective study carried out in the United Kingdom observed the occurrence of earlier menarche in women who were not breastfed.[30] Exclusive breastfeeding was also considered a protective factor for CPP, correlating negatively with this form of PP.[31]

However, there are results that do not associate breastfeeding with PP. In a prospective cohort study, exclusive breastfeeding (for 4 months or more) had no significant effect on the age at peak height velocity (APHV).[32] Lee at al. also found no association between breastfeeding and the onset of puberty in boys (although it did show a protective effect in girls).[33] The presence of disparate results may be due to several factors, with the main ones being the difference in the definition of breastfeeding between the various studies (in relation to the duration of breastfeeding) and the fact that this parameter is subject to recall bias by the participants.

So, despite methodologic differences between the study designs, most studies have verified a protective effect of breastfeeding on PP. This can be explained by the association between breastfeeding and weight gain in childhood, since the

first is inversely related to the second.[28] Obesity and overweight can lead to an increase in leptin, a possible trigger for the onset of puberty, as well as an increase in the concentration of insulin-like growth factor I (IGF-1), which may also be associated with PP.[26, 29] Furthermore, children who are breastfed have a slower growth pattern than those who are formula-fed.[29] (Table 4, Appendix C)

2.2. Formula feeding

Although infant formulas are constantly being reformulated to resemble breast milk as closely as possible,[34] there are still some differences, especially in terms of nutrient content.[23]

Infant formulas have a higher protein content and, therefore, a higher IGF-1 content,[35] consequently leading to an increase in insulin concentration in infants.[28] As a result, there is an increase in adipose tissue,[28, 30, 35] weight gain and higher risk of developing obesity,[35] all predictors of a PP, as seen above. The higher energy density of formula compared to breast milk can also be a factor in the development of obesity.[23] In addition, the use of a bottle does not allow the infant to regulate satiety correctly.[23, 28] These data, together with those found on breastfeeding, suggest that formula feeding may contribute to the development of PP.

In fact, there are several types of infant formula, one of which is based on soy protein. They are useful when there is a diagnosis of cow's milk protein allergy, lactose intolerance or if the parents follow a vegan diet.[34] The use of this formulas is still controversial, due to its phytoestrogen content and the role of these compound in pubertal development.[36] While some studies find no association between soy consumption and the early development of some pubertal

markers,[36, 37] others identify a positive link with the occurrence of PP.[31] The mixed results do not allow a definitive conclusion to be drawn, and it is not yet possible to be certain about the long-term effects of exposure to soy phytoestrogens.[36] Therefore, more studies are needed. (Table 5, Appendix D)

3. Energy intake and body composition in the timing of puberty

The energy density of the child's diet will influence pre-pubertal body composition and, perhaps, the timing of puberty.

Tuck Seng Cheng et al. found a positive association between higher total energy intake (TEI) and earlier voice breaking in boys, as well as precocious menarche, breast development and PHV in girls.[4] Higher TEI was also associated with earlier menarche in other study.[12] In contrast, Koprowski et al. found that a higher TEI contributed to a delay in menarche. However, the authors believe that this negative association was due to an under-reporting of dietary intake by a specific population with the highest Quetelet Index.[38] A low energy intake also seems to influence pubertal development. As seen above, a deficient energy intake seems to impact kisspeptin system.[2, 5, 23] A study carried out on rodents showed that a negative energy balance caused inhibition of kisspeptin gene expression, with a consequent delay in pubertal development.[39] Moreover, ghrelin (a hormone associated with energy insufficiency) seems to exert an inhibitory effect on the release of gonadotropins and decrease the stimulating effect of GnRH on LH.[26]

Regarding pre-pubertal body composition, several studies have already examined its effect on pubertal development. In a study with boys and girls between the ages of 2 and 7 years old, it was observed that children who were obese had an earlier APHV.[17] Similarly, Suutela et al. found that, at the age of 9

years old, for every 1kg/m^2 increase in body mass index (BMI), there was a decrease of 1,7 and 1,3 months in APHV, in girls and boys respectively.[40] Another study conducted in Sweden showed that a greater increase of BMI during childhood (from 2 to 8 years of age) was related to PP.[41] In addition, Anton and colleagues also showed that the onset of puberty was earlier in overweight or obese children than in normal-weight or underweight ones (3,5 months earlier for girls and 3 months for boys).[42]

On the other hand, Buyken et al. exhibited that pre-pubertal body composition had a more significant influence on pubertal markers associated with a later stage of puberty (AHPV and age at menarche), but not those related to the beginning of this stage (ATO).[43] Particularly for boys, the positive association between obesity and overweight on CPP was only found when this BMI classification lasted for more than 2 years.[44]

As can be seen, most studies point to a positive relationship with higher TEI and higher BMI during childhood on PP. This association may be explained due to an increase in adipose tissue resulting from a positive energy balance, with a consequent increase in the levels of leptin and insulin, mediators of the onset of puberty.[4, 12, 45] In addition, estrogen biosynthesis also occurs in adipose tissue, so an increase in this tissue (a possible consequence of a higher TEI and an increase in the BMI) could result in a higher concentration of this hormone and PP.[12, 45] (Table 6, Appendix E)

4. The role of nutrients intake in precocious puberty

4.1. Macronutrients

Protein

The exact mechanisms linking protein intake to puberty have yet to be described. A longitudinal study carried out in the United Kingdom with boys and girls revealed that an additional 500 kcal intake from protein was associated with earlier breast development (2,5 years earlier), as well as earlier PHV (1,69 years) and menarche (1,4 years) in girls. This higher protein intake was also associated with the appearance of pubic hair in both boys (2,94 years earlier) and girls (2,49 years earlier).[4] In agreement with these findings, Nguyen et al. found that, for girls with more than 8 years with a BMI equal or greater than 18.5 kg/m^2, a higher protein intake (more 1.1 g/day) was linked with a higher risk of a precocious onset of menarche.[12]

Regarding protein source, evidence suggest that animal protein intake is inversely associated with the pubertal development markers APHV and ATO in boys and girls[46] and with age of menarche[12],but was positively associated with a higher concentration of estrogen (more precisely estrone).[47] However, there was no association with the age of onset of breast, genital and pubic hair development.[46] On another note, replacing 10g of animal protein with plant protein showed a lower risk of menarche[48] and, reinforcing these results, Xiong et al. found that higher soy consumption was related to later puberty in both sexes.[49] Nevertheless, other studies have already pointed to an association between soy intake and an increased risk of CPP.[31] Indeed, these divergent results may be due to the fact that the studies had different designs, either retrospective or prospective, but also different periods of soy intake, with one of

the studies focusing on the first months of life (using infant formula) and the other two on childhood and pubertal period.

As mentioned above, although the exact mechanism has yet to be described, there are some theories that link protein intake with pubertal development. In fact, the intake of this macronutrient in childhood is important for promoting adiposity rebound before the onset of puberty.[23] This second increase in the BMI curve usually occurs between the ages of 6 and 8 and, if it starts earlier, can be an indicator of obesity[50] which is linked to PP, as we saw earlier.[17-19] In addition, a high protein intake seems to stimulate the production of IGF-1[35], which in turn appears to be one of the factors responsible for the secretion of GnRH, involved in pubertal development mechanism.[4, 12] Furthermore, the increase in the intake of this macronutrient can lead to hyperinsulinemia and insulin resistance, which are responsible for increasing the bioavailability of sex hormones (especially in females)[4] and are present in the majority of girls with PP.[51] The differences seen between boys and girls may also suggest a sexual dysmorphism in protein metabolism.[4] (Table 7, Appendix F)

Carbohydrates

In studies carried out in female populations, disparate results were found by Koprowski et al. and Meng et al. The first authors couldn't identify any association between carbohydrate intake and the age of menarche,[38] while the others found that a higher intake of this macronutrient was positively related to a later age of menarche.[52] When studying the effect of carbohydrate consumption on pubertal development in both sexes, Cheng and his colleagues found no association.[4]

In the specific case of sugar-sweetened beverages, Carwile et al. realised that consumption of more than 1,5 servings of sugar-sweetened beverages per day represented an earlier onset of menarche by 2,7 months, compared to those who consumed these beverages less than twice a week.[53] In addition, a high-glycaemic diet seems to stimulate premature activation of GnRH by inducing low-grade inflammation in the hypothalamus.[54]

With regard to dietary fibre, studies show that its consumption is associated with a later onset of menarche[12, 55] and breast development.[47, 55] Moreover, higher insoluble fibre intake was associated with lower oestradiol concentrations.[47] A possible explanation for these associations is that, in general, fibre-rich foods contain a considerable amount of isoflavones, which are responsible for limiting endogenous estrogen synthesis and possibly delaying the onset of puberty.[12, 45, 47]

The specific effect of carbohydrates on pubertal development is not yet well explained. On one hand, we know that a high intake of carbohydrates can lead to an increase in weight and BMI, factors that we have already seen that influence pubertal timing.[17, 40-42] On the other hand, the role of this macronutrient in PP can possibly be explained by its hypothesised negative influence on estrogen metabolism.[12] (Table 8, Appendix G)

Fat

Xu et al. found that a higher total intake of this macronutrient was linked to an earlier puberty timing, as well as higher intake of polyunsaturated fatty acids (PUFAs).[56] Similar results were found by Nguyen and colleagues, with a positive association between a higher intake of PUFAs and a precocious onset of puberty.[12] Also for females, replacing saturated fatty acids with PUFAs in the diet

was associated with earlier puberty timing, as well as higher concentrations of dihomo-gamma-linolenic acid (a PUFA) and palmitoleic acid (a monounsaturated fatty acid (MUFA)) were.[57] Evidence has also been found that a high-fat diet can induce an inflammatory state in the hypothalamus and consequent premature activation of GnRH.[54]

On the other hand, in other studies no association was found between pubertal development and total fat intake[4] or, more specifically, the total intake of MUFAs.[57] There are also authors who report an association between the intake of MUFAs and a delay in the onset of menarche.[12] Xu et al. thought they had found a possible positive association between a higher intake of MUFAs and earlier breast development and menarche, however this association was eliminated when adjustments were made for protein intake. Bearing in mind that MUFAs typically come from foods such as red meat, eggs and milk, this could mean that the positive association found between this type of fatty acid and PP may actually be due to the protein content of the food sources.[56]

This difference in results between the role of MUFA intake and the role of plasma concentrations of palmitic acid in pubertal development, may be due to the fact that MUFAs are obtained not only from the diet, but also endogenously from saturated fatty acids.[57] In the case of the evidence found on PUFAs, the exact mechanisms that elucidate their association with PP have not yet been found. One of the hypotheses put forward is the involvement of PUFAs in stimulating mammary gland development.[56]

This could lead us to believe that dietary fat plays a key role in PP. However, all this different evidence does not allow us to draw a firm conclusion, and more

studies are needed on the role played by each fatty acid on pubertal development. (Table 9, Appendix H)

4.2. Micronutrients

During puberty, micronutrient needs are increased[58] so it will be crucial to have a good pre-pubertal intake in order to ensure normal pubertal development. Different micronutrients appear to play an important role in pubertal timing.

According to scientific evidence, one of the reasons for the compromised iron status of pubertal girls is the loss of this micronutrient with menstruation. For girls with a low iron intake (<9 mg/day), the onset of menarche seems to have an adverse effect on serum ferritin. On the other hand, girls who had a higher habitual iron intake or who took supplements of this micronutrient maintained their iron stores even during menstruation.[59] Another investigation shows that a higher iron intake seems to be associated with an earlier menarche.[12]

Villamor and colleagues found an association between vitamin D deficiency and precocious menarche. The mechanisms that try to explain this theory are based on the possible increase in obesity and/or leptin and IGF-1 concentrations, when there is vitamin D deficiency.[60] Furthermore, a more advanced pubertal stage seems to be a risk factor for vitamin D deficiency.[61] (Table 10, Appendix I)

Critical analysis

This narrative review aimed to gather evidence on the complex association between nutrition and pubertal timing and development.

However, we recognise some limitations. Firstly, this study design adopts a less formal methodological approach. As such, it may have some impact on the results found. In addition, the indicators used to assess the onset of puberty, and its

development were not the same in all the studies included. In fact, some secondary sexual characteristics may be more associated with the beginning of pubertal development (such as breast development), while others are related to the end of this stage (such as menarche). Also, most of the studies in this review found results only associated with females and did not assess all ethnicities, which doesn't allow us to generalise the results. Regarding the role of nutrition, the dietary assessment methods were not the same for all the studies, and it was not always possible to evaluate the effect of a macronutrient and/or micronutrient alone, considering the synergism between them. Finally, there are other factors that influence pubertal development and have not always been considered, such as birth weight, socioeconomic environment and physical activity.

Despite these limitations, this study allows us to understand the various aspects in which nutrition plays an important role in pubertal development. The involvement of nutritionists and their close monitoring of pubertal development is crucial to avoid the tendency towards PP and its complications.

Conclusions

In summary, scientific evidence shows that there is a link between nutrition and the timing of puberty and development. In the case of breastfeeding, in addition to the health benefits for the infant, it also seems to have a protective effect on PP. On the other hand, an increase in BMI, energy intake and protein intake during childhood seems to have a positive link with PP. More studies are needed, especially those with a longitudinal and prospective design and also covering the male sex, to understand the impact of nutrients throughout pubertal development and so that specific nutritional recommendations can be developed.

References

1. Hosokawa M, Imazeki S, Mizunuma H, Kubota T, Hayashi K. Secular trends in age at menarche and time to establish regular menstrual cycling in Japanese women born between 1930 and 1985. BMC Womens Health. 2012; 12:19.
2. Farello G, Altieri C, Cutini M, Pozzobon G, Verrotti A. Review of the Literature on Current Changes in the Timing of Pubertal Development and the Incomplete Forms of Early Puberty. Front Pediatr. 2019; 7:147.
3. Plant TM. Neuroendocrine control of the onset of puberty. Front Neuroendocrinol. 2015; 38:73-88.
4. Cheng TS, Sharp SJ, Brage S, Emmett PM, Forouhi NG, Ong KK. Longitudinal associations between prepubertal childhood total energy and macronutrient intakes and subsequent puberty timing in UK boys and girls. Eur J Nutr. 2022; 61(1):157-67.
5. Calcaterra V, Cena H, Regalbuto C, Vinci F, Porri D, Verduci E, et al. The Role of Fetal, Infant, and Childhood Nutrition in the Timing of Sexual Maturation. Nutrients. 2021; 13(2)
6. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970; 45(239):13-23.
7. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969; 44(235):291-303.
8. Kleanthous K, Papadimitriou DT, Gryparis A, Papaevangelou V, Papadimitriou A. A Mixed-Longitudinal Study of Height Velocity of Greek Schoolchildren and the Milestones of the Adolescent Growth Spurt. Children (Basel). 2022; 9(6)
9. Pereira A, Ferrer P, Binder A, Rojas J, Michels KB, Corvalán C, et al. Association Between Markers of Adiposity During Childhood and Puberty Onset in Latino Girls. J Clin Endocrinol Metab. 2023; 108(11):e1272-e81.
10. Ong KK, Bann D, Wills AK, Ward K, Adams JE, Hardy R, et al. Timing of voice breaking in males associated with growth and weight gain across the life course. J Clin Endocrinol Metab. 2012; 97(8):2844-52.
11. Harries ML, Walker JM, Williams DM, Hawkins S, Hughes IA. Changes in the male voice at puberty. Arch Dis Child. 1997; 77(5):445-7.
12. Nguyen NTK, Fan HY, Tsai MC, Tung TH, Huynh QTV, Huang SY, et al. Nutrient Intake through Childhood and Early Menarche Onset in Girls: Systematic Review and Meta-Analysis. Nutrients. 2020; 12(9)
13. Tang J, Xue P, Huang X, Lin C, Liu S. Diet and Nutrients Intakes during Infancy and Childhood in Relation to Early Puberty: A Systematic Review and Meta-Analysis. Nutrients. 2022; 14(23)
14. Cheng TS, Day FR, Lakshman R, Ong KK. Association of puberty timing with type 2 diabetes: A systematic review and meta-analysis. PLoS Med. 2020; 17(1):e1003017.
15. Ohlsson C, Bygdell M, Nethander M, Kindblom JM. Early puberty and risk for type 2 diabetes in men. Diabetologia. 2020; 63(6):1141-50.
16. Day FR, Elks CE, Murray A, Ong KK, Perry JR. Puberty timing associated with diabetes, cardiovascular disease and also diverse health outcomes in men and women: the UK Biobank study. Sci Rep. 2015; 5:11208.
17. Chen LK, Wang G, Bennett WL, Ji Y, Pearson C, Radovick S, et al. Trajectory of Body Mass Index from Ages 2 to 7 Years and Age at Peak Height Velocity in Boys and Girls. J Pediatr. 2021; 230:221-29.e5.

18. Neville KA, Walker JL. Precocious pubarche is associated with SGA, prematurity, weight gain, and obesity. Arch Dis Child. 2005; 90(3):258-61.
19. Ahmed ML, Ong KK, Dunger DB. Childhood obesity and the timing of puberty. Trends Endocrinol Metab. 2009; 20(5):237-42.
20. Berkey CS, Frazier AL, Gardner JD, Colditz GA. Adolescence and breast carcinoma risk. Cancer. 1999; 85(11):2400-9.
21. Moss AR, Osmond D, Bacchetti P, Torti FM, Gurgin V. Hormonal risk factors in testicular cancer. A case-control study. Am J Epidemiol. 1986; 124(1):39-52.
22. Kaltiala-Heino R, Marttunen M, Rantanen P, Rimpelä M. Early puberty is associated with mental health problems in middle adolescence. Soc Sci Med. 2003; 57(6):1055-64.
23. Calcaterra V, Verduci E, Magenes VC, Pascuzzi MC, Rossi V, Sangiorgio A, et al. The Role of Pediatric Nutrition as a Modifiable Risk Factor for Precocious Puberty. Life (Basel). 2021; 11(12)
24. Uenoyama Y, Inoue N, Nakamura S, Tsukamura H. Central Mechanism Controlling Pubertal Onset in Mammals: A Triggering Role of Kisspeptin. Front Endocrinol (Lausanne). 2019; 10:312.
25. Quinton ND, Smith RF, Clayton PE, Gill MS, Shalet S, Justice SK, et al. Leptin binding activity changes with age: the link between leptin and puberty. J Clin Endocrinol Metab. 1999; 84(7):2336-41.
26. Abreu AP, Kaiser UB. Pubertal development and regulation. Lancet Diabetes Endocrinol. 2016; 4(3):254-64.
27. WHO Guidelines Approved by the Guidelines Review Committee. In: Guideline: Protecting, Promoting and Supporting Breastfeeding in Facilities Providing Maternity and Newborn Services. Geneva: World Health Organization Copyright © World Health Organization 2017.; 2017.
28. Aghaee S, Deardorff J, Greenspan LC, Quesenberry CP, Jr., Kushi LH, Kubo A. Breastfeeding and timing of pubertal onset in girls: a multiethnic population-based prospective cohort study. BMC Pediatr. 2019; 19(1):277.
29. Al-Sahab B, Adair L, Hamadeh MJ, Ardern CI, Tamim H. Impact of breastfeeding duration on age at menarche. Am J Epidemiol. 2011; 173(9):971-7.
30. Morris DH, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ. Determinants of age at menarche in the UK: analyses from the Breakthrough Generations Study. Br J Cancer. 2010; 103(11):1760-4.
31. Felício JS, de Alcântara AL, Janaú LC, de Moraes LV, de Oliveira M, de Lemos MN, et al. Association of Soy and Exclusive Breastfeeding With Central Precocious Puberty: A Case-Control Study. Front Endocrinol (Lausanne). 2021; 12:667029.
32. Karaolis-Danckert N, Buyken AE, Sonntag A, Kroke A. Birth and early life influences on the timing of puberty onset: results from the DONALD (DOrtmund Nutritional and Anthropometric Longitudinally Designed) Study. Am J Clin Nutr. 2009; 90(6):1559-65.
33. Lee M, Kim J, Kim H, Shin J, Suh J. Early life factors of precocious puberty based on Korean nationwide data. Sci Rep. 2025; 15(1):16165.
34. Cristina Pinto da C, Filipa M-M, Victoria B. Fórmulas Infantis: indicação, função e constituição. Acta Portuguesa de Nutrição. 2021(27):18-23.
35. Socha P, Grote V, Gruszfeld D, Janas R, Demmelmair H, Closa-Monasterolo R, et al. Milk protein intake, the metabolic-endocrine response, and growth in

infancy: data from a randomized clinical trial. Am J Clin Nutr. 2011; 94(6 Suppl):1776s-84s.
36. Strom BL, Schinnar R, Ziegler EE, Barnhart KT, Sammel MD, Macones GA, et al. Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood. Jama. 2001; 286(7):807-14.
37. Sinai T, Ben-Avraham S, Guelmann-Mizrahi I, Goldberg MR, Naugolni L, Askapa G, et al. Consumption of soy-based infant formula is not associated with early onset of puberty. Eur J Nutr. 2019; 58(2):681-87.
38. Koprowski C, Ross RK, Mack WJ, Henderson BE, Bernstein L. Diet, body size and menarche in a multiethnic cohort. Br J Cancer. 1999; 79(11-12):1907-11.
39. Navarro VM. Metabolic regulation of kisspeptin - the link between energy balance and reproduction. Nat Rev Endocrinol. 2020; 16(8):407-20.
40. Suutela M, Hero M, Kosola S, Miettinen PJ, Raivio T. Prenatal, newborn and childhood factors and the timing of puberty in boys and girls. Pediatr Res. 2024; 96(3):799-804.
41. He Q, Karlberg J. Bmi in childhood and its association with height gain, timing of puberty, and final height. Pediatr Res. 2001; 49(2):244-51.
42. Holmgren A, Niklasson A, Nierop AF, Gelander L, Aronson AS, Sjöberg A, et al. Pubertal height gain is inversely related to peak BMI in childhood. Pediatr Res. 2017; 81(3):448-54.
43. Buyken AE, Karaolis-Danckert N, Remer T. Association of prepubertal body composition in healthy girls and boys with the timing of early and late pubertal markers. Am J Clin Nutr. 2009; 89(1):221-30.
44. Liu G, Guo J, Zhang X, Lu Y, Miao J, Xue H. Obesity is a risk factor for central precocious puberty: a case-control study. BMC Pediatr. 2021; 21(1):509.
45. Cheng G, Buyken AE, Shi L, Karaolis-Danckert N, Kroke A, Wudy SA, et al. Beyond overweight: nutrition as an important lifestyle factor influencing timing of puberty. Nutr Rev. 2012; 70(3):133-52.
46. Remer T, Shi L, Buyken AE, Maser-Gluth C, Hartmann MF, Wudy SA. Prepubertal adrenarchal androgens and animal protein intake independently and differentially influence pubertal timing. J Clin Endocrinol Metab. 2010; 95(6):3002-9.
47. Biro FM, Summer SS, Huang B, Chen C, Benoit J, Pinney SM. The Impact of Macronutrient Intake on Sex Steroids During Onset of Puberty. J Adolesc Health. 2022; 70(3):483-87.
48. Moslehi N, Asghari G, Mirmiran P, Azizi F. Longitudinal association of dietary sources of animal and plant protein throughout childhood with menarche. BMC Pediatr. 2021; 21(1):206.
49. Xiong J, Xu Y, Liu X, Wang X, Shan S, Crabbe MJC, et al. Prospective association of dietary soy and fibre intake with puberty timing: a cohort study among Chinese children. BMC Med. 2022; 20(1):145.
50. Pomi AL, Pepe G, Aversa T, Corica D, Valenzise M, Messina MF, et al. Early adiposity rebound: predictors and outcomes. Ital J Pediatr. 2024; 50(1):98.
51. Ibáñez L, Potau N, Zampolli M, Riqué S, Saenger P, Carrascosa A. Hyperinsulinemia and decreased insulin-like growth factor-binding protein-1 are common features in prepubertal and pubertal girls with a history of premature pubarche. J Clin Endocrinol Metab. 1997; 82(7):2283-8.
52. Meng X, Li S, Duan W, Sun Y, Jia C. Secular Trend of Age at Menarche in Chinese Adolescents Born From 1973 to 2004. Pediatrics. 2017; 140(2)

53. Carwile JL, Willett WC, Spiegelman D, Hertzmark E, Rich-Edwards J, Frazier AL, et al. Sugar-sweetened beverage consumption and age at menarche in a prospective study of US girls. Hum Reprod. 2015; 30(3):675-83.
54. Valsamakis G, Arapaki A, Balafoutas D, Charmandari E, Vlahos NF. Diet-Induced Hypothalamic Inflammation, Phoenixin, and Subsequent Precocious Puberty. Nutrients. 2021; 13(10)
55. de Ridder CM, Thijssen JH, Van 't Veer P, van Duuren R, Bruning PF, Zonderland ML, et al. Dietary habits, sexual maturation, and plasma hormones in pubertal girls: a longitudinal study. Am J Clin Nutr. 1991; 54(5):805-13.
56. Xu Y, Xiong J, Gao W, Wang X, Shan S, Zhao L, et al. Dietary Fat and Polyunsaturated Fatty Acid Intakes during Childhood Are Prospectively Associated with Puberty Timing Independent of Dietary Protein. Nutrients. 2022; 14(2)
57. Cheng TS, Day FR, Perry JRB, Luan J, Langenberg C, Forouhi NG, et al. Prepubertal Dietary and Plasma Phospholipid Fatty Acids Related to Puberty Timing: Longitudinal Cohort and Mendelian Randomization Analyses. Nutrients. 2021; 13(6)
58. Villamor E, Jansen EC. Nutritional Determinants of the Timing of Puberty. Annu Rev Public Health. 2016; 37:33-46.
59. Ilich-Ernst JZ, McKenna AA, Badenhop NE, Clairmont AC, Andon MB, Nahhas RW, et al. Iron status, menarche, and calcium supplementation in adolescent girls. Am J Clin Nutr. 1998; 68(4):880-7.
60. Villamor E, Marin C, Mora-Plazas M, Baylin A. Vitamin D deficiency and age at menarche: a prospective study. Am J Clin Nutr. 2011; 94(4):1020-5.
61. Tolppanen AM, Fraser A, Fraser WD, Lawlor DA. Risk factors for variation in 25-hydroxyvitamin D_3 and D_2 concentrations and vitamin D deficiency in children. J Clin Endocrinol Metab. 2012; 97(4):1202-10.

Appendix

Appendix index

Appendix A: Overview of the physiological mechanisms of the onset of puberty

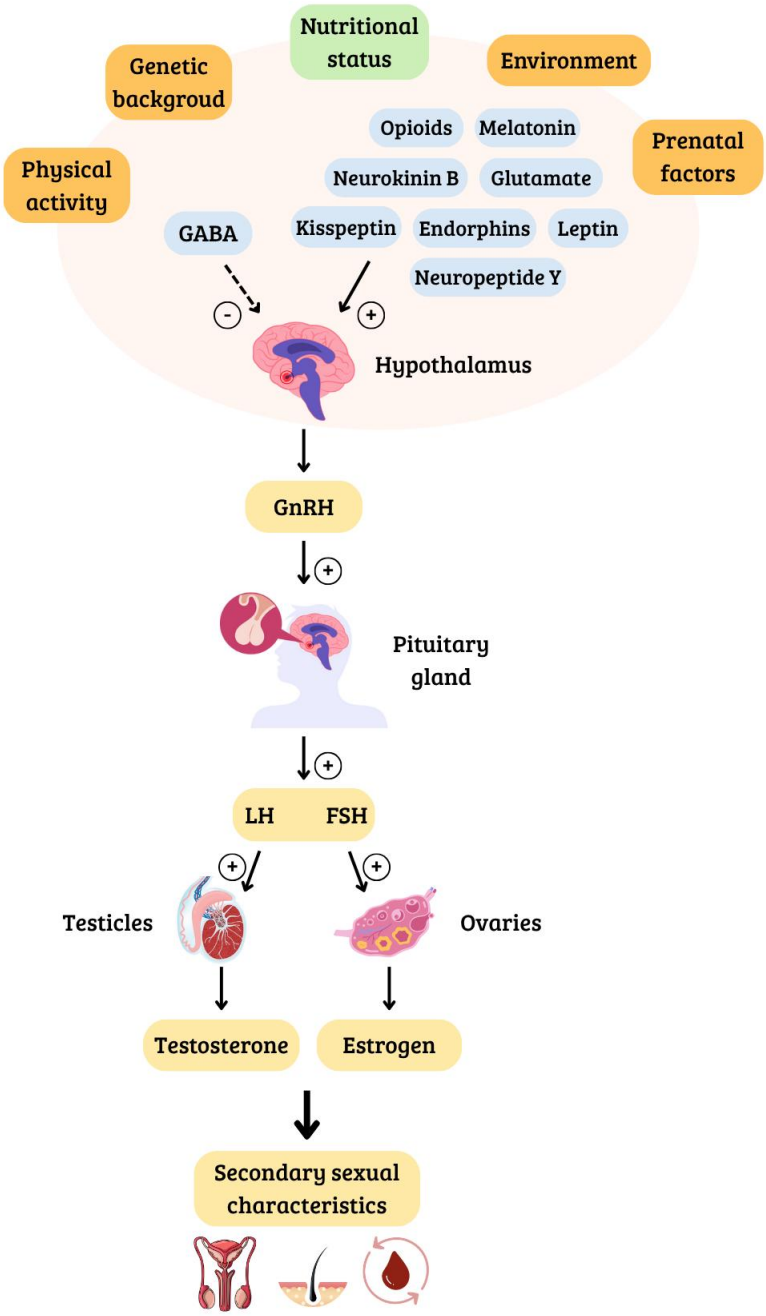

Figure 1 - Physiological mechanisms of the onset of puberty.

Appendix B: Tanner Scale

Pubic Hair Scale (both males and females)

Table 1 - Tanner Scale for pubic hair development

Stage	Clinical Description
I	No pubic hair
II	Downy hair
III	Scant terminal hair
IV	Terminal hair that fills the entire triangle overlying the pubic region
V	Terminal hair that extends beyond the inguinal crease onto the thigh

Adapted from: Guidi JCA, Sapra A. Physiology, Sexual Maturity Rating. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022

Female Breast Development Scale

Table 2 - Tanner Scale for breast development

Stage	Clinical Description
I	No glandular breast tissue palpable
II	Breast bud palpable under the areola (**First pubertal sign in females**)
III	Breast tissue palpable outside areola; no areolar development
IV	Areola elevated above the contour of the breast, forming a “double scoop” appearance
V	The areolar mound recedes into a single breast contour with areolar hyperpigmentation, papillae development, and nipple protrusion

Adapted from: Guidi JCA, Sapra A. Physiology, Sexual Maturity Rating. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022

Male External Genitalia Scale

Table 3 - Tanner Scale for genital development

Stage	Clinical Description
I	Testicular volume < 4 ml or long axis < 2.5 cm
II	Testicular volume 4 ml-8 ml or long axis 2.5 to 3.3 cm long (**First pubertal sign in males**)
III	Testicular volume 9 ml-12 ml or long axis 3.4 to 4.0 cm long
IV	Testicular volume 15-20 ml or long axis 4.1 to 4.5 cm long
V	Testicular volume > 20 ml or long axis > 4.5 cm long)

Adapted from: Guidi JCA, Sapra A. Physiology, Sexual Maturity Rating. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022

Appendix C: Detailed characterisation of the included studies on the effect of breastfeeding on pubertal development

Table 4 - Detailed characterisation of the included studies on the effect of breastfeeding on pubertal development

Study	Study design	Sample description	Pubertal development markers used	Main results
Aghaee et. al (2019)[28]	Prospective cohort study	3331 mother-daughter pairs (girls were born between 2004 and 2006)	TS (the onset of puberty was defined as the transition from stage 1 to stage 2)	Girls who were not breastfed were more likely to experience: • earlier thelarche (HR:1.25; **95%CI: 1.07 to 1.46**) • earlier pubarche (HR: 1.24; **95%CI: 1.05 to 1.46**) compared with girls who were breast fed for ≥ 6 months
Al-Sahab et. al (2011)[29]	Multiethnic population-based prospective cohort study	994 Filipino girls born in 1983–1984	Self-reported age at menarche	An increase in 1 month of exclusive breastfeeding decreased the risk of attaining earlier menarche by 6% (HR:0,94; 95%CI: 0.90 to 0.98; **p<0.01**)
Felício et. al (2021)[31]	Retrospective case-control study	161 girls (84 diagnosed with CPP and 77 that had a normal pubertal development)	Diagnosis with CPP	Exclusive breastfeeding for more than 6 months was associated with a reduction of likelihood of having PP (OR=0.5; 95%CI: 0.3 to 0.9; **p=0.05**) and correlated negatively with the presence of CPP
Karaolis-Danckert et. al (2009)[32]	Prospective cohort study	215 participants	ATO, APHV and menarche	Exclusive breastfeeding for 4 months or more had no significant effect on APHV (p=0.5)
Lee et. al (2025)[33]	Retrospective cohort study	898701 children (43952 with CPP)	Diagnosis with CPP	Breastfeeding exerted a significant protective effect against CPP in girls (OR=0.95; 95%CI: 0.93 to 0.98; **p=0.003**) but not in boys (p=0.11)
Morris et. al (2010)[30]	Retrospective cohort study	81606 women aged from 16 to 98 years old	Self-reported age ate menarche	Menarche occurred earlier in women who were not breastfed (**p=0.03**)

Definition of abbreviations: ATO, age at take-off; APHV, age at peak height velocity; CPP, Central Precocious Puberty; PP, Precocious Puberty; TS, Tanner Scale.

Appendix D: Detailed characterisation of the included studies on the effect of formula feeding on pubertal development

Table 5 - Detailed characterisation of the included studies on the effect of formula feeding on pubertal development

Study	Study design	Sample description	Pubertal development markers used	Main results
Felício et al. (2021)[31]	Retrospective case-control study	161 girls (84 diagnosed with CPP and 77 that had a normal pubertal development)	Diagnosis with CPP	The use of soy-based formulas increased the likelihood of having CPP (OR=3.8; 95%CI:1.5 to 9; **p<0.05**) and correlated positively with the presence of CPP (r=0.2; **p<0.01**)
Sinai et. al (2019)[37]	Nested case–control (based on a prospectively followed cohort)	89 children (44 males) from the original 2004–2006 cohort	TS (PP was defined as Tanner stage 2 before the age of 8 years in females and 9 years in males)	There was no association between the consumption of soy and the incidence of precocious puberty (p=0.54)
Socha et. al (2011)[35]	Randomized controlled clinical trial	1138 healthy, formula-fed infants	Serum concentrations of IGF-1	Compared with the breastfed group, serum concentrations of IGF-1 free, IGF-1 total and IGF-binding protein2 were increased in the formula groups (**p<0.001**)
Strom et. al (2001)[36]	Retrospective cohort study	811 subjects (248 were fed soy formula and 563 were fed cow milk formula during infancy)	Self-reported pubertal maturation and menstrual reproductive history	No statistically significant differences were observed for either women or men for any pubertal outcomes. For women: • Age at menarche (95%CI: -0.32 to 0.26) For men: • Age when voice changed (95%CI: -0.09 to 0.67) • Age when hair appeared on chest/face/pubic area (95%CI: -0.19 to 0.59)

Definition of abbreviations: CPP, Central Precocious Puberty; IGF-1, insulin-like growth factor I; PP, precocious puberty; TS, Tanner Scale.

Appendix E: Detailed characterisation of the included studies on the effect of energy intake and body composition on pubertal development

Table 6 - Detailed characterisation of the included studies on the effect of energy intake and body composition on pubertal development

Study	Study design	Sample description	Pubertal development markers used	Main results
Buyken et. al (2009)[43]	Prospective cohort study	215 participants of the *Dortmund Nutritional and Anthropometric Longitudinally Designed* (DONALD) *Study*	Genital (G2) or breast (B2) development in boys and girls, respectively, age at menarche, ATO and APHV	Prepubertal BMI clearly predicted: • APHV in both sexes (girls: **p=0.01**; boys: **p=0.046**) • puberty duration in both sexes (girls: **p<0.0001**; boys: **p=0.01**) • and age at menarche in girls (**p=0.03**)
Chen et. al (2021)[17]	Prospective birth-cohort study	1296 mother-child dyads (663 boys and 633 girls), predominantly Black and low-income	APHV	Obesity at 2 to 4 years old was associated with earlier APHV in: • boys (β= −0.19; 95%CI: −0.35 to −0.03; **p<0.05**) • and girls (β= −0.22; 95%CI: −0.37 to −0.07; **p<0.01**) Obesity at 5 to 7 years was associated with earlier APHV in: • boys (β= −0.18; 95%CI: −0.32 to −0.03; **p<0.05**) • and girls (β= −0.27; 95%CI: −0.40 to −0.13; **p<0.001**) Overweight at 5 to 7 years was associated with earlier APHV in: • girls (β= −0.24; 95%CI: −0.40 to −0.08; **p<0.01**)

Cheng et. al (2022)[4]	Prospective cohort study	7730 children (3811 boys and 3919 girls)	Genital (G2) or breast (B2) development in boys and girls, respectively, voice breaking, age at menarche, age at PH and AH development and APHV	For boys, higher TEI (more 500kcal) was associated with: • Earlier voice breaking (ß= −0.29; 95%CI: −0.50 to −0.07; **p=0.009** For girls, higher TEI was associated with: • Earlier breast development (ß= −0.28; 95% CI = −0.46 to − 0.10; **p=0.003**) • Earlier APHV (ß= −0.15; 95%CI: −0.26 to −0.04; **p=0.008**) • Earlier menarche (ß= −0.14; 95%CI: −0.27 to −0.01; **p=0.04**)
He et. al (2001)[41]	Prospective population-based cohort study	3650 full-term and healthy Swedish children	APHV	• An increase of 1 BMI unit between 2 and 8 years of age was associated, on average, with a 0,11 years earlier age of PHV for the two sexes (**p<0.05**) • For the full range of BMI change in childhood of this study, the effect on the timing of puberty was as large as 0,6 years in boys and 0,7 years in girls
Holmgren et. al (2017)[42]	Prospective cohort study	1901 boys and girls from *GrowUp1990 Gothenburg birth cohort*	APHV	APHV was: • 3,2 months earlier in overweight/obese girls (95%CI: -0.49 to -0.16; **p<0.001**) • 2,6 months earlier in overweight/obese boys (95%CI: -0.42 to -0.11; **p<0.001**) comparing with normal-weight or underweight children
Koprowski et. al (1999)[38]	Prospective multiethnic cohort study	1378 girls aged from 8 to 13 years old	Age at menarche	• High TEI (> 12013 kJ) versus low TEI (< 7004 kJ) was associated with a delay in menarche (RH=0.7; 95%CI: 0.5 to 0.9; **p<0.001**) • However, when Hispanic girls from the highest Quetelet's index category were excluded, energy intake was not a significant predictor of menarche in this ethnic group (p=0.08)

Liu et. al (2021)[44]	Retrospective case-control study	846 children diagnosed with CPP and randomly sampled 1650 healthy control subjects	Diagnose with CPP	Girls with overweight and obesity for: • 1 to 2 years (aOR=1.65; 95%CI: 1.10 to 2.77; **p=0.01**) • 2 to 3 years (aOR=2.01; 95%CI: 1.54 to 2.86; **p=0.0002**) • more than 3 years (aOR=2.48; 95%CI: 1.67 to 3.72; **p=0.0001**) were at high risk for CPP than normal weight ones. Boys with overweight and obesity for more than 3 years (aOR=2.01; 95%CI: 1.24 to 3.68; **p=0.01**) were at high risk for CPP than normal weight ones.
Nguyen et. al (2020)[12]	Systematic review and meta-analysis	16 longitudinal studies involving 10884 girls in total	Menarche onset	Higher intake of energy was associated with the risk of an earlier onset of menarche (RR=3.32; **95%CI: 1.74 to 6.34**)
Suutela et. al (2024)[40]	Prospective population-based cohort study	4826 girls and 5112 boys born between 1997 and 2002	PHV	Increase in BMI at the age of 9 years old by 1kg/m^2, led to: • 1,7 months earlier age at PHV in girls (95%CI = −1.9 to −1.6; **p<0.001**) • 1,3 months earlier age at PHV in boys (95%CI= −1.4 to −1.1; **p<0.001**)

Definition of abbreviations: ATO, age at take-off; APHV, age at peak height velocity; AH, axillary hair; BMI, body mass index; CPP, Central Precocious Puberty; IGF-1, insulin-like growth factor I; PHV, peak height velocity; PP, precocious puberty; PH, pubic hair; TS, Tanner Scale; TEI, total energy intake.

Appendix F: Detailed characterisation of the included studies on the effect of protein intake on pubertal development

Table 7 - Detailed characterisation of the included studies on the effect of protein intake on pubertal development

Study	Study design	Sample description	Pubertal development markers used	Main results
Biro et al. (2022)[47]	Prospective cohort study	260 girls of Cincinnati puberty study cohort of the *Breast Cancer and the Environment Research Program*	Serum measurements at 6-month intervals for estrogen and sex hormone binding globulin concentrations (18 months prior to onset of puberty, assessment by stage 2 of TS for breast development (B2))	Values of estrone at onset of puberty were associated with total protein (**p=0.038**) and animal protein intake (**p=0.048**)
Cheng et. al (2022)[4]	Prospective cohort study	7730 children (3811 boys and 3919 girls)	Genital (G2) or breast (B2) development in boys and girls, respectively, voice breaking, age at menarche, age at PH and AH development and APHV	For boys, higher protein intake (more 500kcal) was associated with earlier: • Earlier PH development (ß= -2.94; **95%CI: −5.07 to −0.80**) For girls, higher protein intake was associated with: • Earlier breast development (ß= -2.52; 95%CI: −4.45 to −0.59; **p=0.010**) • Earlier APHV (ß= -1.69; 95%CI: −2.81 to −0.57; **p=0.003**) • Earlier menarche (ß= -1.40; 95%CI: −2.79 to −0.02; **p=0.047**) • Earlier PH development (ß= -2.49; **95%CI: −4.43 to −0.56**)
Felício et al. (2021)[31]	Retrospective case-control study	161 girls (84 diagnosed with CPP and 77 that had a normal pubertal development)	Diagnosis with CPP	The use of soy-based formulas increased the likelihood of having CPP (OR=3.8; 95%CI: 1.5 to 9; **p<0.05**) and correlated positively with the presence of CPP (r=0.2; **p<0.01**)

Moslehi et al. (2021)[48]	Prospective cohort study	241 girls aged from 6 to 18 years old from *The Tehran Lipid and Glucose Study*	Onset of menarche	Substituting 10g of animal protein with plant protein was associated with a 16% lower risk of onset of menarche (**p=0.006**)
Nguyen et. al (2020)[12]	Systematic review and meta-analysis	16 longitudinal studies involving 10884 girls in total	Menarche onset	• High total protein intake was associated with a higher risk of earlier onset of menarche (RR=3.2; **95%CI: 2.9 to 3.4**) • Girls with BMI ≥18.5Kg/m^2 that had an earlier onset of menarche, had a higher average protein intake (nearly more 1.1 g/day) (**95%CI: 0.5 to 1.7**) • Girls that had an earlier onset of menarche had higher intake of animal protein (MD=1.4; 95%CI: 0.7 to 2.1; **p<0.001)**
Remer et. al (2010)[46]	Prospective cohort study	109 healthy Caucasian children	ATO, APHV, age at menarche, age at voice breaking, genital (G2) or breast (B2) development in boys and girls, respectively, and PH	For both genders, animal protein intake was negatively associated with: • ATO (**p=0.02**) • APHV (**p=0.04**) There was no association between animal protein intake and: • Genital/breast development (p=0.1) • PH development (p=0.3) • Age at menarche/voice breaking (p=0.07)
Xiong et al. (2022)[49]	Prospective cohort study	4781 children (2152 girls and 2629 boys) aged from 6 to 8 years old from the *Chinese Adolescent Cohort Study*	Genital (G2) or breast (B2) development in boys and girls, respectively, PH development for both genders and age at menarche/voice break	Among girls and boys, higher soy intake was associated with later puberty timing: • Later breast development (**p=0.02)** • Later age at menarche (**p=0.01**) • Later genital development (**p=0.03**) • Later age at voice break (**p=0.02**)

Definition of abbreviations: ATO, age at take-off; APHV, age at peak height velocity; AH, axillary hair; CPP, Central Precocious Puberty; MD, mean difference; PHV, peak height velocity; PP, precocious puberty; PH, pubic hair; TS, Tanner Scale.

Appendix G: Detailed characterisation of the included studies on the effect of carbohydrate intake on pubertal development

Table 8 - Detailed characterisation of the included studies on the effect of carbohydrate intake on pubertal development

Study	Study design	Sample description	Pubertal development markers used	Main results
Biro et. al (2022)[47]	Prospective cohort study	260 girls of Cincinnati puberty study cohort of the *Breast Cancer and the Environment Research Program*	Serum measurements at 6-month intervals for estrogen and sex hormone binding globulin concentrations (18 months prior to onset of puberty, assessment by stage 2 of TS for breast development (B2))	• Higher total fibre intake was correlated with later age of B2 (Spearman Rho=0.165; **p=0.008**) • Higher insoluble fibre intake was associated with lower estradiol levels (**p=0.029**)
Carwile et. al (2015)[53]	Prospective cohort study	5583 girls aged from 9 to 14 years old at baseline, who were part of the *Growing up Today Study* (GUTS)	Self-reported age at menarche	• Girls who consumed >1.5 servings of SSB/day were 26% more likely to attain menarche in the next month, compared with girls who consumed ≤2 servings of SSB, weekly (95%CI: 1.15 to 1.38; **p<0.001**) • Girls who consumed >1.5 servings of SSB/day reported an earlier onset of menarche by 2.7 months than girls who consumed ≤2 servings of the SSB, weekly (**95%CI: -4.1 to -1.3**)
Cheng et. al (2022)[4]	Prospective cohort study	7730 children (3811 boys and 3919 girls)	Genital (G2) or breast (B2) development in boys and girls, respectively, voice breaking, age at menarche, age at PH and AH development and APHV	Total carbohydrate intake was not associated with any pubertal development marker for boys • Age at G2 (p=0.173) • APHV (p=0.981) • Age at voice breaking (p=0.231) or girls • Age at B2 (p=0.543) • APHV (p=0.208) • Age at the onset of menarche (p=0.820)

Koprowski et. al (1999)[38]	Prospective multiethnic cohort study	1378 girls aged from 8 to 13 years old	Age at menarche	Carbohydrate intake was unrelated to age at menarche (p=0.90)
Meng et. al (2017)[52]	Prospective cohort study	3199 Chinese girls aged from 6 to 18 years old who participated in the *China Health and Nutrition Survey* (CHNS	Age at menarche	Girls with higher carbohydrate intake (accounting for more than 65% of total energy) had a lower risk of early menarche (HR=0.62; 95%CI: 0.57 to 0.68: **p<0.01**) compared to those with normal carbohydrate intake (HR=0.95; 95%CI: 0.87–1.04: **p<0.01**)
Nguyen et. al (2020)[12]	Systematic review and meta-analysis	16 longitudinal studies involving 10884 girls in total	Menarche onset	Increased fibre consumption (>25.48g/day) was associated with a decreased risk of earlier onset of menarche (RR=0.83; **95%CI: 0.69 to 1.00**)
Ridder et. al (1991)[55]	Prospective cohort study	63 apparently healthy Caucasian schoolgirls from Utrecht	Breast development (B2), PH development, age at menarche and blood hormone concentrations (estradiol, FSH, LH and sex hormone binding globulin)	Breast development (**p<0.05**) and the onset of menarche (**p<0.05**) occurred sooner in girls with lower fibre intake
Valsamakis et. al (2021)[54]	Narrative review	-	Genital (G2) or breast (B2) development in boys and girls, respectively, PH development, age at menarche and hormone concentrations (sex steroid hormones, FSH, LH, GnRH and serum leptin)	A high-glycaemic-index diet induces a low-grade hypothalamic inflammation and subsequent premature GnRH activation

Definition of abbreviations: APHV, age at peak height velocity; AH, axillary hair; FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinizing hormone; PHV, peak height velocity; PP, precocious puberty; PH, pubic hair; SSB, sugar-sweetened beverages; TS, Tanner Scale.

Appendix H: Detailed characterisation of the included studies on the effect of fat intake on pubertal development

Table 9 - Detailed characterisation of the included studies on the effect of fat intake on pubertal development

Study	Study design	Sample description	Pubertal development markers used	Main results
Cheng et. al (2021)[57]	Mixed-method study (Prospective cohort and Mendelian randomization analysis)	7526 children (3654 boys and 3872 girls) from the *Avon Longitudinal Study of Parents and Children* (ALSPAC)	Genital (G2) or breast (B2) development in boys and girls, respectively, voice breaking, onset of menarche and APHV	For girls, a 5% substitution of saturated fatty acids for PUFA was associated with: • Earlier age at B2 (95%CI: -1.31 to -0.25; **p=0.004**) • Earlier APHV (95%CI: -0.72 to -0.09; **p=0.011**) For girls, higher concentrations of dihomo-gamma-linolenic acid and palmitoleic acid were associated with: • Earlier age at B2 (95%CI: -0.16 to -0.02; **p=0.011** and 95%CI: -0.20 to -0.06; **p=0.0.00011**) • Earlier APHV (95%CI: -0.11 to -0.03; **p=0.00063** and 95%CI: -0.10 to -0.02; **p=0.001**) • Earlier onset of menarche (95%CI: -0.11 to -0.01; **p=0.018** and 95%CI: -0.11 to -0.01**; p=0.017**) No associations were found for boys (p>0.05)
Cheng et. al (2022)[4]	Prospective cohort study	7730 children (3811 boys and 3919 girls)	Genital (G2) or breast (B2) development in boys and girls, respectively, age at voice breaking, age at menarche and age at PH and AH development	Total fat intake was not associated with any pubertal development marker for boys • Age at G2 (p=0.428) • APHV (p=0.910) • Age at voice breaking (p=0.490) or girls • Age at B2 (p=0.627) • APHV (p=0.082) • Age at the onset of menarche (p=0.673)

Nguyen et. al (2020)[12]	Systematic review and meta-analysis	16 longitudinal studies involving 10884 girls in total	Menarche onset	Girls that had an earlier onset of menarche, consumed more 0.5g/day of PUFAs (95%CI: 0.2 to 0.8; **p<0.05**)
Valsamakis et. al (2021)[54]	Narrative review	-	Genital (G2) or breast (B2) development in boys and girls, respectively, PH development, age at menarche and hormone concentrations (sex steroid hormones, FSH, LH GnRH and serum leptin)	A high-fat diet induces a low-grade hypothalamic inflammation and subsequent premature GnRH activation
Xu et. al (2022)[56]	Prospective cohort study	5920 children from *China Health and Nutrition Survey* (CHNS) and *Southwest China Childhood Nutrition and Growth* (SCCNG) *Study* (3425 girls and 2495 boys)	Genital (G2) or breast (B2) development in boys and girls, respectively, and age at menarche/voice breaking	MUFA intake was significantly associated with: • Earlier breast development (B2) (HR=1.10; 95%CI: 1.04 to 1.18; **p=0.04**) • Earlier onset of menarche (HR=1.11; 95%CI: 1.06 to 1.17; **p=0.05**) However, when the models further adjusted for dietary protein intake, these associations were attenuated and no longer statistically significant (p>0.05)

Definition of abbreviations: APHV, age at peak height velocity; AH, axillary hair; FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinizing hormone; MUFA, monounsaturated fatty acid; PHV, peak height velocity; PP, precocious puberty; PH, pubic hair; PUFA, polyunsaturated fatty acids.

Appendix I: Detailed characterisation of the included studies on the effect of micronutrient intake on pubertal development

Table 10 - Detailed characterisation of the included studies on the effect of micronutrient intake on pubertal development

Study	Study design	Sample description	Pubertal development markers used	Main results
Ilich-Ernst et. Al (1998)[59]	Randomized controlled trial (double-blind)	354 healthy, white girls aged from 8 to 13 years old	Pubertal stage was self-assessed by the participants, using illustrations that represent different stages of breast and PH development, on a scale from 1 to 5 (1 indicates preadolescence and 5 adulthood)	• In girls with low iron intake (≤9.5mg/day), the onset of menarche seems to have a negative effect on ferritin levels. In contrast, girls with high iron intake (≥19.4mg/day) maintained their iron reserves after the onset for menarche (**p<0.018**)
Nguyen et. al (2020)[12]	Systematic review and meta-analysis	16 longitudinal studies involving 10884 girls in total	Menarche onset	Girls that had a higher iron intake had a 20% increased risk of experiencing earlier menarche (RR=1.20; **95%CI: 1.03 to 1.40**)
Tolppanen et. al (2012)[61]	Prospective cohort study	7560 children from the *Avon Longitudinal Study of Parents and Children* (ALSPAC)	TS (parental reports regarding breast and PH development)	A more advanced pubertal stage was associated with lower serum 25(OH)D levels. For Tanner stage 2: • Lower serum 25(OH)D3 risk factor was 24% (**95%CI: -0.33 to -0.15**) • Lower serum 25(OH)D2 risk factor was 4% (**95%CI: -0.08 to 0.00**) For Tanner stages 3 to 5: • Lower serum 25(OH)D3 risk factor was 48% (**95%CI: -0.60 to 0.36**) • Lower serum 25(OH)D2 risk factor was 10% (**95%CI: -0.15 to -0.05**)

Villamor et. al (2011)[60]	Prospective cohort study	242 girls from Colombia	Age at menarche	• 57% of the girls that belonged to the vitamin D-deficient group (25(OH)D<50nmol/L) reached menarche during follow-up in contrast with 23% of the girls in the vitamin D–sufficient group (25(OH)D≥75nmol/L) (**p=0.0004**) • Girls who were vitamin D–deficient had nearly twice the risk of reaching menarche compared to vitamin D–sufficient ones (HR= 2.05; 95%CI: 1.03 to 4.07; **p=0.04**)

Definition of abbreviations: PH, pubic hair; TS, Tanner Scale