Response to Letter to the Editor from De Zegher and Ibanes: On the rising incidence of early breast development

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We thank Francis de Zegher and Lourdes Ibanez (1) for their interest in our study on patients with isolated central precocious puberty (CPP) (2) and their proposal of an additional explanation for the findings. They suggest that the mismatch between birth weight and BMI SDS at CPP diagnosis in the three subgroups investigated (familial, sporadic and adopted patients) might help to explain the precocious onset of puberty and is consistent with the findings of epidemiological studies showing that rapid postnatal weight gain is associated with early age at menarche (3) and that the trend towards earlier pubertal onset observed in girls in many countries runs parallel to a trend towards increasing BMI and obesity rates (4).

CPP results from early activation of the hypothalamic-pituitary-gonadal axis and follows the same sequence as physiological puberty. The precise signal responsible for initiating puberty remains unknown, but genetic, environmental and nutritional factors all play an important role in pubertal timing (5). As discussed in our article, the transition from a poor nutritional environment to a more adequate nutritional environment can trigger puberty in some adopted children. However, a moderately high BMI SDS, of about 1 SDS, has been reported for most patients presenting with CPP, regardless of CPP etiology. CPP may be isolated, or attributable to pathological conditions, such as tumours, malformations, or associated with some syndromic disorders. Patients with such 'organic' forms of CPP have a moderately high BMI SDS at CPP diagnosis, similar to that of patients with isolated forms of CPP (6, 7, 8). In addition, studies of patients with monogenic CPP due to makorin RING finger protein 3 (MKRN3) loss of

function, affecting the regulation of the hypothalamo-pituitary-gonadal axis, have also been reported to have a BMI SDS at the presentation that is moderately high and similar to that of patients with isolated and idiopathic CPP (9, 10).

We acknowledge that the early phase of CPP is characterized by an acceleration of height velocity, but the pattern of change of BMI during this period is unclear, and the changes in body composition occurring during this crucial phase of puberty onset cannot be ignored. In girls, puberty is associated with a change in body composition, with an increase in percentage body fat (11). In precocious puberty, these changes occur early and, at diagnosis, fat mass SDS has already increased (12, 13). Clearly, the normative data for BMI used to calculate BMI SDS mostly include data for children with a normal puberty onset, and the use of these data in populations of patients with precocious puberty, therefore, essentially constitutes a comparison of the adiposity of a population of children with early pubertal changes in body composition with that in prepubertal children. Therefore, in our opinion, the 'mismatch' between birth characteristics and BMI SDS at diagnosis is a consequence, rather than a cause, of early pubertal development and its effects on body composition.

It is not possible to deduce the underlying mechanism from these data, but they suggest that the onset of precocious puberty is linked to a higher BMI, regardless of early postnatal weight gain. The association of BMI and precocious puberty onset has not been studied in detail directly, but a larger gain in BMI during childhood,

between the ages of two and eight years, is known to be related to an earlier onset of puberty (14), and higher BMI SDS and fat mass percentage during childhood, between the ages of four and seven years, have been shown to be associated with a higher risk of precocious puberty in boys, regardless of BMI at birth (15). Further studies of this association would greatly increase our understanding of the modification of body composition just before (or around) the onset of puberty.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this article.

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References

- de Zegher F & Ibáñez L. On the rising incidence of early breast development: puberty as an adaptive escape from ectopic adiposity in mismatch girls. *European Journal of Endocrinology* 2021 **185** L1–L2. (<https://doi.org/10.1530/EJE-21-0287>)
- Harbulot C, Lessim S, Simon D, Martinerie L, Storey C, Ecosse E, De Roux N, Carel JC & Léger J. Prevalence and clinical characteristics of isolated forms of central precocious puberty: A cohort study at a single academic center. *European Journal of Endocrinology* 2021 **184** 243–251. (<https://doi.org/10.1530/EJE-20-0862>)
- Sloboda DM, Hart R, Doherty DA, Pennell CE & Hickey M. Age at menarche: influences of prenatal and postnatal growth. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 46–50. (<https://doi.org/10.1210/jc.2006-1378>)
- Eckert-Lind C, Busch AS, Petersen JH, Biro FM, Butler G, Brauner EV & Juul A. Worldwide secular trends in age at pubertal onset assessed by breast development among girls: a systematic review and meta-analysis. *JAMA Pediatrics* 2020 **174** e195881. (<https://doi.org/10.1001/jamapediatrics.2019.5881>)
- Abreu AP & Kaiser UB. Pubertal development and regulation. *Lancet: Diabetes and Endocrinology* 2016 **4** 254–264. ([https://doi.org/10.1016/S2213-8587\(15\)00418-0](https://doi.org/10.1016/S2213-8587(15)00418-0))
- Trivin C, Couto-Silva AC, Sainte-Rose C, Chemaillot W, Kalifa C, Doz F, Zerah M & Brauner R. Presentation and evolution of organic central precocious puberty according to the type of CNS lesion. *Clinical Endocrinology* 2006 **65** 239–245. (<https://doi.org/10.1111/j.1365-2265.2006.02582.x>)
- Mogensen SS, Aksglaede L, Mouritsen A, Sorensen K, Main KM, Gideon P & Juul A. Diagnostic work-up of 449 consecutive girls who were referred to be evaluated for precocious puberty. *Journal of Clinical Endocrinology and Metabolism* 2011 **96** 1393–1401. (<https://doi.org/10.1210/jc.2010-2745>)
- Wannes S, Elmaleh-Berges M, Simon D, Zenaty D, Martinerie L, Storey C, Gelwane G, Paulsen A, Ecosse E, De Roux N *et al.* High prevalence of syndromic disorders in patients with non-isolated central precocious puberty. *European Journal of Endocrinology* 2018 **179** 373–380. (<https://doi.org/10.1530/EJE-18-0613>)
- Simon D, Ba I, Mekhail N, Ecosse E, Paulsen A, Zenaty D, Houang M, Jesuran Perelroizen M, de Filippo GP, Salerno M *et al.* Mutations in the maternally imprinted gene MKRN3 are common in familial central precocious puberty. *European Journal of Endocrinology* 2016 **174** 1–8. (<https://doi.org/10.1530/EJE-15-0488>)
- Seraphim CE, Canton APM, Montenegro L, Piovesan MR, Macedo DB, Cunha M, Guimaraes A, Ramos CO, Benedetti AFF, de Castro Leal A *et al.* Genotype-phenotype correlations in central precocious puberty caused by MKRN3 mutations. *Journal of Clinical Endocrinology and Metabolism* 2021 **106** 1041–1050. (<https://doi.org/10.1210/clinem/dgaa955>)
- Boot AM, Bouquet J, de Ridder MA, Krenning EP & de Muinck Keizer-Schrama SM. Determinants of body composition measured by dual-energy X-ray absorptiometry in Dutch children and adolescents. *American Journal of Clinical Nutrition* 1997 **66** 232–238. (<https://doi.org/10.1093/ajcn/66.2.232>)
- Boot AM, De Muinck Keizer-Schrama S, Pols HA, Krenning EP & Drop SL. Bone mineral density and body composition before and during treatment with gonadotropin-releasing hormone agonist in children with central precocious and early puberty. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 370–373. (<https://doi.org/10.1210/jcem.83.2.4573>)
- van der Sluis IM, Boot AM, Krenning EP, Drop SL & de Muinck Keizer-Schrama SM. Longitudinal follow-up of bone density and body composition in children with precocious or early puberty before, during and after cessation of GnRH agonist therapy. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 506–512. (<https://doi.org/10.1210/jcem.87.2.8202>)
- He Q & Karlberg J. Bmi in childhood and its association with height gain, timing of puberty, and final height. *Pediatric Research* 2001 **49** 244–251. (<https://doi.org/10.1203/00006450-200102000-00019>)
- Pereira A, Busch AS, Solares F, Baier I, Corvalan C & Mericq V. Total and central adiposity are associated with age at gonadarche and incidence of precocious gonadarche in boys. *Journal of Clinical Endocrinology and Metabolism* 2021 **106** 1352–1361. (<https://doi.org/10.1210/clinem/dgab064>)

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