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2530-0180/

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Reply to the comment to our article titled: "Association of metabolic syndrome with low birth weight of birth, intake hypercaloric diets and acanthosis nigricans in childhood and teens with overweight and obesity"[☆]



Respuesta al comentario a nuestro artículo titulado: «Asociación del síndrome metabólico con bajo peso al nacimiento, consumo de dietas hipercalóricas y acantosis nigricans en escolares y adolescentes con sobrepeso y obesidad»

Dear Editor,

With regard to the comments on our article entitled: "Association of metabolic syndrome with low birth weight, intake of high-calorie diets and acanthosis nigricans in children and adolescents with overweight and obesity",¹ we should like to make the following points:

Observational studies should be assessed using the guidelines of the *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE) statement,²⁻⁵ as recommended by the Cochrane Center,⁵ which states that in case-control designs, "the eligibility criteria and the sources and methods to determine the cases and select the controls" should be provided, but does not mention as a prerequisite "an a priori selection", which would be methodologically better, but is not indispensable for this design. However, the eligibility criteria are discussed below.

According to Argimon Pallas and Jiménez Villa,⁶ in case-control studies, cases are taken from a series of patients in whom the disease has already been diagnosed and who are available for the study. The study was conducted in ambulatory obese children who attended a hospital. Children with metabolic syndrome were the cases,

while those without the syndrome were used as controls. Potential exposure factors, including low birth weight, a history of intake of high-calorie diets and acanthosis nigricans, were identified and considered retrospective factors. Even if this is not considered to be a case-control study, it is an analytical cross-sectional study, and odds ratio calculation is also applicable. In our opinion, however, the study has the basic structure of a case-control design because it is retrospective and longitudinal, and because there is a time period between the consequence (metabolic syndrome) and exposure factors, which are retrospective (e.g. low birth weight).

As regards exposure criteria, they were defined in the article as follows: low birth weight according to the World Health Organization criteria,⁷ high-calorie diets using the criteria of the American Academy of Pediatric Nutrition,⁸ and acanthosis nigricans according to the Simone et al. criteria.⁹ The commentators disagree with our criteria, but give no particulars.

In the study discussion, we state in the first paragraph that the study population came from a third level hospital, and that this was why there was a high rate of metabolic syndrome. However, "selection or Berkson's bias occurs when the combination of exposure and the disease under study increases the chance of hospital admission".² In our case, the frequency of exposure would be higher in these cases than in hospital controls. Thus, at least as regards "low birth weight", we think that it does not increase their chance of hospital admission at 10 and 15 years of age. Moreover, obese children and adolescents were not admitted to hospital, but were ambulatory and attended an overweight and obesity program.

As regards acanthosis nigricans, we recognize its scientific (both clinical and biochemical) relationship to insulin resistance, mentioned in the text, but acanthosis nigricans has not been shown to be a definite marker of insulin resistance, as explained by Zhu et al.,¹⁰ and is therefore not considered a confounding variable. The authors cite Chiarpenello et al., who reported that 60% of the population had high insulin levels with a gradual increase in the prevalence of acanthosis nigricans, but this is not a sufficient pathological or epidemiological explanation for regarding acanthosis nigricans as a marker of insulin resistance. Consistent evidence is lacking.

The most important concept in this study is the association of fetal programming and the development of metabolic changes, which other authors have considered (Barker's theory). In particular, birth weight has a special relevance for Mexican women, but it should be admitted that retrospective studies, such as case-control studies,

[☆] Please cite this article as: Velazquez-Bautista M, López-Sandoval JJ, González-Hita M, Vázquez-Valls E, Cabrera-Valencia IZ, Torres-Mendoza BM. Respuesta al comentario a nuestro artículo titulado: «Asociación del síndrome metabólico con bajo peso al nacimiento, consumo de dietas hipercalóricas y acantosis nigricans en escolares y adolescentes con sobrepeso y obesidad». *Endocrinol Diabetes Nutr.* 2017;64:568-569.

use risk factors present in the past, and these designs potentially have a recall bias; more robust studies, such as cohort studies, would be better for validation.

Our study identified the eligibility criteria for a high-calorie diet, and reported how dietary intake was assessed. The average intake of two days per week was estimated by nutritionists, using validated, standardized three-dimensional products, among other aspects reported. However, the authors state that this is not an adequate method, and cite Ferrari as the recommended guide. A considerable part of our work agrees with the Ferrari recommendations. However, this paper does not mention the high-calorie diets discussed, which cannot be evaluated with a dietary intake. We agree that the assessment of dietary intake involves many aspects, but the Ferrari study was neither a systematic review nor a meta-analysis, and is therefore not conclusive as an international guideline for dietary intake, and even less for high-calorie diets.

Observational studies, and particularly this case-control or analytical cross-sectional study, are not conclusive with regard to the cause-effect relationship; in fact, as regards the robustness of the guidelines, they are considered to be at a level different to that of cohort studies, and for practical purposes, the evidence from case-control or analytical cross-sectional designs usually groups them at the same level, so that the change to an analytical cross-sectional study does not change the level of evidence or the odds ratios.⁶

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2530-0180/

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