Breast-Feeding Modulates the Influence of the Peroxisome Proliferator-Activated Receptor-\(\gamma\) (PPARG2) Pro12Ala Polymorphism on Adiposity in Adolescents

The Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) cross-sectional study

**OBJECTIVE** — The peroxisome proliferator–activated receptor-\(\gamma\)2 (PPARG2) Pro12Ala polymorphism has been associated with a higher BMI and a lower risk of type 2 diabetes in adulthood. The association between adiposity and PPARG variants can be influenced by environmental factors such as early growth, dietary fat, and (as recently shown) breast-feeding. The objectives of this study were to assess 1) the influence of the PPARG2 Pro12Ala polymorphism on adiposity markers in adolescents and 2) a possible modulating effect of breast-feeding on these associations.

**RESEARCH DESIGN AND METHODS** — Data on breast-feeding duration, BMI, and genotypes for the Pro12Ala polymorphism were available for 945 adolescents (mean age 14.7 years). The breast-feeding duration was obtained from parental reports. We measured weight, height, waist circumference, and six skinfold thicknesses.

**RESULTS** — No significant associations between the Pro12Ala polymorphism and any of the above-mentioned anthropometric parameters were found. There were significant interactions between the PPARG2 Pro12Ala polymorphism and breast-feeding with regard to adiposity measurements (all adjusted \(P < 0.05\)). Indeed, in children who had not been breast-fed, Ala12 allele carriers had higher adiposity parameters (e.g., Δ BMI +1.88 kg/m\(^2\); adjusted for age, sex, and center; \(P = 0.007\)) than Pro12Pro adolescents. In contrast, in breast-fed subjects, there was no significant difference between Ala12 allele carriers and Pro12Pro children in terms of adiposity measurements, whatever the duration of breast-feeding.

**CONCLUSIONS** — Breast-feeding appears to counter the deleterious effect of the PPARG2 Pro12Ala polymorphism on anthropometric parameters in adolescents.
sitivity (6), suggesting that if this variant does influence obesity predisposition, it may do so through context-dependent mechanisms. This finding illustrates the importance of appropriate stratification of analyses by environmental or other genetic factors when PPARG variants are studied. More consistently, the Pro12Ala polymorphism has been associated with a lower risk of type 2 diabetes in a meta-analysis of genome-wide association studies (7).

Data in children are scarcer. In 311 Finnish children aged 7 years, the Ala12 allele was associated with a higher ponderal index at birth and higher waist circumference in adulthood, relative to those for Pro12Pro subjects (8). In Greek girls aged 3–4 years, adiposity was higher in Ala12 allele carriers than in Pro12Pro carriers (9).

Eriksson (10) showed that the well-known association existing between low birth weight and insulin resistance later in life was seen only in Pro12Pro individuals. Moreover, Meirihaeghe et al. (11) showed that individuals carrying the Ala12 allele had a lower birth weight (due to shorter gestational duration and a higher risk of preterm birth) than Pro12Pro subjects. However, this result was not confirmed in 5,652 individuals from the Northern Finland Birth Cohort of 1966 (12). Labayen et al. (13) showed that low birth weight may program a lower fat-free mass in adolescents carrying the Ala12 allele.

Last, certain environmental factors (such as dietary fat and physical activity) interact with the effect of the PPARG polymorphism on adiposity. Mook-Kanamori et al. (14) showed that the growth rate from birth to 18 months of age was higher in Ala12Ala carriers than in Pro12Pro carriers when the duration of breast-feeding was between 0 and 4 months, whereas the Pro12Ala polymorphism was not associated with an early growth rate in infants breast-fed for longer than 4 months.

The aims of the present study were to 1) assess the influence of the PPARG2 Pro12Ala polymorphism on BMI, waist circumference, and the sum of six skinfold thicknesses in a sample of 945 European adolescents and 2) test the modulating effect of breast-feeding on these associations.

RESEARCH DESIGN AND METHODS — The current report is based on data derived from the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) cross-sectional study, the aim of which was to obtain a broad range of standardized, reliable, and comparable nutrition- and health-related data from a random sample of European adolescents aged 12.5–17.5 years. Data collection took place during 2006 and 2007 in 10 European cities. A detailed description of the HELENA study sampling has been published elsewhere (15).

All of the adolescents meeting the general HELENA inclusion criteria and having data for age, sex, and BMI were considered in the final sample (n = 3,546). To investigate biochemical assays and genetic analyses, one-third of the cohort was randomly selected for blood collection (resulting in a total of 1,155 subjects). Of the latter, the 945 adolescents with data on the PPARG2 Pro12Ala polymorphism and BMI and breast-feeding information were included in the present study.

After receiving comprehensive information on the study’s aims and methods, all adolescents and their parents or guardians signed informed consent forms. The study was performed according to the ethical guidelines of the Edinburgh revision of the 1961 Declaration of Helsinki (2000), good clinical practice, and the legislation on clinical research in each of the participating countries. The protocol was approved by the investigational review boards at the participating university medical centers.

The harmonized, standardized anthropometric measurements were strictly monitored. Participants were barefoot and in underwear, and anthropometric measurements were taken by trained researchers. Weight was measured with an electronic set of scales (Type SECA 861; precision 0.05 kg) and height was measured in the Frankfort plane with a height gauge (Type SECA 225; precision 1 mm). Waist circumference was measured with a nonelastic tape (Seca 200; precision 1 mm) to the nearest 0.1 cm. Skinfold thicknesses were measured at the left biceps, triceps, subscapular area, suprailiac area, thigh, and calf with a Holtain caliper (precision 0.2 mm), according to Lohman’s anthropometric standardization reference manual. The overall score was calculated by summing the six skinfold thicknesses. Mean skinfolds and circumferences were calculated from three consecutive measurements.

Identification of sexual maturation (Tanner and Whitehouse stages I–V) was assessed by a physician. Weight and height at birth and the durations of gestation and breast-feeding were collected via a parental questionnaire. The duration of gestation was stratified into three categories: <35, between 35 and 40, and >40 weeks. The total duration of breast-feeding was recoded from six categories into four: never, <3, 3–5, and ≥6 months. The duration of exclusive breast-feeding (defined by the World Health Organization as no liquid or solid nutrition other than breast milk) was recoded in a similar manner.

A uniaxial accelerometer (ActiGraph GT1M, Pensacola, FL; http://www.theactigraph.com) was used to assess physical activity. Adolescents were instructed to place the monitor underneath clothing, at the lower back, using an elastic waistband, and to wear it for 7 consecutive days. They were also instructed to wear the accelerometer during all time awake and only to remove it during water-based activities. At least 3 days of recording with a minimum of 8 h registration/day was set as an inclusion criterion. In this study, the time-sampling interval (epoch) was set at 15 s. A measure of total volume of activity (hereafter called average physical activity) was expressed as the sum of recorded counts per epoch divided by total daily registered time expressed in minutes (counts per minute) (16).

The socioeconomic level was assessed in terms of the maternal educational level and was coded into four categories (elementary, lower secondary, higher secondary, or higher education).

Preparation of genomic DNA from whole blood and genotyping Blood samples were drawn at school after a 10-h, overnight fast and according to a standardized collection protocol; blood for DNA extraction was collected in EDTA K3 tubes. DNA was extracted from white blood cells with the Puregene kit (Qiagen, Courtaboeuf, France) and stored at −20°C. Genotyping of the Pro12Ala polymorphism was performed on an Illumina system using GoldenGate technology (Illumina, San Diego, CA). The genotyping success rate was 99.4%.

Statistical analyses Statistical analyses were performed with SAS software (SAS Institute, Cary, NC). Deviation from Hardy-Weinberg equilibrium was tested using the χ² test (1 degree of freedom). The BMI and the sum of the
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Table 1—Descriptive characteristics of the HELENA study sample

|                                | n   | Value       |
|--------------------------------|-----|-------------|
| **Neonatal data**              |     |             |
| Birth weight (kg)              | 914 | 3.33 ± 0.58 |
| Birth height (cm)              | 882 | 50.4 ± 3.2  |
| Duration of total breast-feeding |    |             |
| Never breast-fed               | 173 | (18.3)      |
| <3 months                      | 279 | (29.5)      |
| 3–5 months                     | 237 | (25.1)      |
| ≥6 months                      | 256 | (27.1)      |
| Duration of pregnancy          |     |             |
| <35 weeks                      | 49  | (5.4)       |
| 35–40 weeks                    | 574 | (63.6)      |
| >40 weeks                      | 280 | (31.0)      |
| **Clinical characteristics**   |     |             |
| Boys                           | 434 | (45.9)      |
| Girls                          | 511 | (54.1)      |
| Pubertal status                |     |             |
| Tanner stage 2                 | 12  | (1.4)       |
| Tanner stage 3/4               | 601 | (67.3)      |
| Tanner stage 5                 | 242 | (26.3)      |
| Age (years)                    | 945 | 14.7 ± 1.4  |
| BMI (kg/m²)                    | 945 | 21.3 ± 3.8  |
| Waist circumference (cm)       | 935 | 72.2 ± 9.3  |
| Sum of 6 skinfolds (mm)        | 887 | 92.0 ± 14.4 |
| Physical activity (cpm)        | 638 | 434 ± 151   |

Data are means ± SD or n (%).

Table 2—Association between the PPARG2 Pro12Ala polymorphism and body composition and neonatal characteristics in the HELENA study

|                          | Pro12Pro | Pro12Ala | Ala12Ala | P*       | X/Ala12 vs. Pro12Pro | Ala12Ala vs. X/Pro12 |
|--------------------------|----------|----------|----------|----------|----------------------|----------------------|
| n                        | 746      | 187      | 12       |          |                      |                      |
| BMI (kg/m²)              | 21.3 ± 3.6 | 21.4 ± 4.3 | 20.2 ± 2.5 | 0.55 | 0.98                 | 0.29                 |
| Waist circumference (cm) | 72.1 ± 9.2 | 72.8 ± 10.0 | 69.8 ± 7.5 | 0.50 | 0.78                 | 0.29                 |
| Sum of 6 skinfolds (mm)  | 92.2 ± 41.1 | 92.5 ± 43.5 | 73.2 ± 24.0 | 0.52 | 0.79                 | 0.31                 |
| Birth weight (kg)        | 3.33 ± 0.57 | 3.34 ± 0.57 | 2.90 ± 1.08 | 0.10†  | 0.43†                | 0.03†                |
| Birth height (cm)        | 50.4 ± 3.1 | 50.4 ± 2.7 | 47.7 ± 6.1 | 0.07†  | 0.43†                | 0.02†                |
| n                        | 689      | 177      | 10       |          |                      |                      |
| Duration of gestation    | n        |          |          |          |                      |                      |
| <35 weeks                | 38 (0.78) | 10 (0.20) | 1 (0.02) |          |                      |                      |
| 35–40 weeks              | 454 (0.79) | 113 (0.20) | 7 (0.01) | 0.98 |                      |                      |
| >40 weeks                | 219 (0.78) | 58 (0.21) | 3 (0.01) |          |                      |                      |

Data are means ± SD or n (frequency). *Adjusted for age, sex, and center. †Adjusted for age, sex, center, and gestational duration.
feeding. It is noteworthy that our analyses yielded similar results when we used the duration of exclusive breast-feeding (data not shown). Furthermore, there were no significant interactions with sex ($P_{/H11005} > 0.90$), and the associations were similar in boys and girls (data not shown).

We performed power calculations in the whole sample ($n_{/H11005} = 945$) using a dominant or a recessive model, and in the non-breast-fed children subsample ($n = 173$) using a dominant model only (Table 3). As an example, the whole sample had sufficient power (>80%) to identify significant effect sizes of at least 0.75 kg/m$^2$ for BMI, 2.1 cm for waist circumference, 9.6 mm for skinfold thicknesses, 140 g for birth weight, and 0.7 cm for birth height using a minor allele frequency of 0.11 under a dominant model.

**CONCLUSIONS** — In the present study, the $PPARG2$ Ala12 allele was associated with higher adiposity indexes (BMI, waist circumference, and the sum of skinfolds) in children who had not been breast-fed. However, this association was not seen in children who had been breast-fed (even for a short period).

Our results are in agreement with those of Mook-Kanamori et al. (14), who showed that the Ala12 allele was associated with increased weight gain in early infancy in non-breast-fed children (14). We observed similar findings for BMI, waist circumference, and skinfolds, even later in life (i.e., adolescence). This result supports the hypothesis whereby breast-feeding has a beneficial effect on the obesity risk later in life in a genetically predisposed group.

Our study illustrates an association between an environmental factor (breast-feeding) and the phenotypic expression of a gene (modulation of anthropometric parameters by $PPARG$) and thus suggests that phenotypes modulated by $PPARG2$ polymorphisms can be influenced by gene-environment interactions early in life. Barker (18) has explained the impact of pre- and postnatal nutrition later in life by the theory of “nutritional programming”: what is beneficial in utero and during the postnatal period in cases of undernutrition could become deleterious in the event of an excessive nutritional environment (i.e., metabolic diseases). The exact mechanisms involved in this type of phenomenon are still subject to speculation; they may begin to operate during fetal life and continue until the early neonatal period. A recent meta-analysis performed by the World Health Organization, including 33 studies, concluded that breast-fed individuals were less likely to be overweight and/or obese in childhood and adolescence (19). Some studies but not all showed a dose-response effect, with a more pronounced effect associated with a long duration of breast-feeding (20). The reason for the absence of a dose-response effect on the

![Figure 1](image-url)

**Figure 1**—A: Mean BMI as a function of the breast-feeding duration in $PPARG2$ Pro12Pro (■) vs. Ala12 allele carriers (□). **$P = 0.007$ (adjusted for age, sex, and center).** B: Mean waist circumference as a function of breast-feeding duration in $PPARG2$ Pro12Pro (■) vs. Ala12 allele carriers (□). *$P = 0.02$ (adjusted for age, sex, and center). C: Mean sum of skinfolds as a function of breast-feeding duration in $PPARG2$ Pro12Pro (■) vs. Ala12 allele carriers (□). *$P = 0.03$ (adjusted for age, sex, and center).
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Table 3—Power calculation for the PPARG2 Pro12Ala polymorphism effects

|                        | Mean Δ using a dominant model | Mean Δ using a recessive model |
|------------------------|-------------------------------|-------------------------------|
| In the HELENA study (n = 945) |                               |                               |
| BMI (kg/m²)            | 0.75                          | 3.15                          |
| Waist circumference (cm)| 2.1                           | 7.7                           |
| Sum of 6 skinfolds (mm)| 9.6                           | 36                            |
| Birth weight (kg)       | 0.14                          | 0.50                          |
| Birth height (cm)       | 0.7                           | 2.8                           |
| In non–breast-fed children (n = 173) |                 |                               |
| BMI (kg/m²)            | 2.1                           | NC                            |
| Waist circumference (cm)| 5.0                           | NC                            |
| Sum of 6 skinfolds (mm)| 23.1                          | NC                            |

NC, not calculated.

PPARG2 Ala12 allele in our study is unclear; one possible explanation is that the programming effect of breast-feeding is more strongly influenced by gene × nutrient interactions at an early age rather than a quantitative process linked to the duration of the exposure.

A number of mechanisms can potentially explain how breast-feeding could counterbalance the deleterious effect of the Ala12 allele in adolescents. It has been shown that the association between dietary fat and BMI is influenced by PPARG2 genotypes. Memisoglu et al. (21) found that monounsaturated fat–rich diets were inversely associated with BMI in Ala12 allele carriers, but the authors did not find any association in Pro12Pro women. Similarly, Luan et al. (22) showed that for a diet with a low polyunsaturated-to-saturated fat ratio, Ala12 allele carriers had a greater BMI than Pro12Pro carriers. Considering that breast milk constitutes a diet with specific fat intake (with a higher proportion of polyunsaturated fatty acids than formula milk [23]), our results seem to be in line with those reported by Luan et al. (22), albeit their study was conducted in adults. Moreover, one potential hypothesis is that breast milk or breast-feeding supplies factors such as prostaglandin J2 (24), a natural ligand. The decrease in PPARG2 transcriptional activity observed in Ala12 allele carriers could be, therefore, compensated for by breast milk. The latter also contains a number of adipokines. It is known that PPARG2 agonists (such as the thiazolidinediones) can downregulate leptin expression (25); however, the presence of this compound in breast and/or formula milk has yet to be established and would require further investigation.

We also showed in the present study that Ala12Ala subjects had a lower body weight (~430 g) and height (~2.7 cm) at birth than subjects carrying the Pro12 allele, independently of the duration of gestation. Although these results need to be considered with caution (as they concern only 12 homozygote children) and replicated, they are in line with previous data. Indeed, in two Irish population samples, we have previously shown that the PPARG2 Ala12 allele was associated with lower birth weight (primarily caused by shorter gestational duration) (11).

The present study has certain limitations. First, the duration of gestation was coded into three categories rather than being specified in weeks and was obtained from questionnaires filled out by the parents (rather than from a national health registry). Therefore, the accuracy of the data on gestational duration needs to be considered with circumspection. Second, the “being small for gestational age” phenotype could not be assessed. However, because the duration of gestation did not influence the effect of the PPARG2 polymorphism in the present study, we believe that this factor did not bias our results. Likewise, we lacked information on singleton or multiple pregnancies, which have different growth patterns. Other factors (such as parental weight status, food preferences, or smoking status) known to influence the effect of breast-feeding on the subject’s subsequent BMI could not be assessed in our study. However, the main factors known to influence fat mass were available and did not alter the observed associations when used as confounders. Third, study center was used as a surrogate estimate of ethnicity, which is not ideal and may induce misclassification. Last, the subgroup of non–breast-fed children was relatively small (n = 173), which might make it prone to identification of false-positive associations. However, we feel confident of our data as they are in line with the data of Mook-Kanamori et al. (14).

In summary, our results suggest that breast-feeding can counterbalance the deleterious impact of the PPARG2 Pro12Ala polymorphism on adiposity in adolescents. These findings confirm the importance of taking account of gene-environment interactions in association studies and the possible effect of early, diet-based prevention programs in population subgroups. At a time when the prevalence of obesity in children and adolescents continues to increase, our results may constitute a new argument in favor of the public health benefits of breast-feeding.

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References
1. Deeb SS, Fajas L, Nemoto M, Phlajamaki J, Mykkänen L, Kuusisto J, Laakso M, Fujimoto W, Auwerx J. A Pro12Ala substitution in PPARG2 associated with decreased receptor activity, lower body mass index and improved insulin sensitivities. Nat Genet 1998;20:284–287
2. Beamer BA, Yen CJ, Andersen RE, Muller D, Elahi D, Cheskin LJ, Andres R, Roth J, Shuldiner AR. Association of the Pro12Ala variant in the peroxisome proliferator-activated receptor-γ2 gene with obesity in two Caucasian populations. Diabetes 1998;47:1806–1808
3. Cole SA, Mitchell BD, Hsieh WC, Pineda P, Beamer BA, Shuldiner AR, Comuzzie
AG, Blangero J, Hixson JE. The Pro12Ala variant of peroxisome proliferator-activated receptor-γ2 (PPAR-γ2) is associated with measures of obesity in Mexican Americans. Int J Obes Relat Metab Disord 2000;24:522–524

4. Meirhaeghe A, Fajas L, Helbecque N, Cottel D, Auswerx J, Deeb SS, Amouyel P. Impact of the peroxisome proliferator activated receptor γ2 Pro12Ala polymorphism on adiposity, lipids and non-insulin-dependent diabetes mellitus. Int J Obes Relat Metab Disord 2000;24:195–199

5. Willer CJ, Spielotes EK, Loos RJ, Li S, Lindgren CM, Heil IM, Bernd JD, Elliot AL, Jackson AU, Lamina C, Lettre G, Lim N, Lyon HN, McCarroll SA, Papadakis K, Qi L, Randall JC, Roccasecca RM, Sanna S, Scheet P, Weedon MN, Wheeler E, Zhao JH, Jacobs LC, Prokopenko I, Soranzo N, Tanaka T, Timpson NJ, Almgren P, Bennett A, Bergman RN, Bingham SA, Bonnycastle LL, Brown M, Burti NP, Chines P, Coin L, Collins FS, Connell JM, Cooper C, Smith GD, Dennis EM, Deodhar P, Elliott P, Erdos MR, Estrada K, Evans DM, Gianniny L, Gieger C, Gillson CJ, Guiducci C, Hackett R, Hadley D, Hall AS, Havulinna AS, Hebebrand J, Hofman A, Isomaa B, Jaddoe VW, Jukema M, AVENA Study Group. Effect of the Pro12Ala allele in the PPARγ2 gene on the relationship between birth weight and body composition in adolescents: the AVENA study. Pediatr Res 2007;62:615–619

6. Tonjes A, Scholz M, Loeflter M, Stumvoll M. Association of Pro12Ala polymorphism in peroxisome proliferator-activated receptor γ with pre-diabetic phenotypes: meta-analysis of 57 studies on nondiabetic individuals. Diabetes Care 2006;29:2489–2497

7. Zeggini E, Scott LJ, Saxena R, Voight BF, Marchini JL, Hu T, de Bakker PI, Abecasis GR, Almgren P, Andersen G, Ardlie K, Boström KB, Bergman RN, Bonnycastle LL, Borch-Johnsen K, Burti NP, Chen H, Chines PS, Daly MJ, Deodhar P, Ding CJ, Doney AS, Duren WL, Elliott KS, Erdos MR, Frayling TM, Freathy RM, Gianniny L, Grallert H, Graupn U, Groves CJ, Guiducci C, Hansen T, Herder C, Hitman GA, Hughes TE, Isomaa B, Jackson AU, Jergensen T, Kong A, Kubalanza K, Kuruvilla FG, Kuusisto J, Langenberg C, Lango H, Lauritzen T, Li Y, Lindgren CM, Lysenko V, Marville AF, Meisinger C, Midttjell K, Mohlke KL, Morken MA, Morris AD, Nalisin P, Precision MR, Reid AJ, Remer R, Renstrom E, Reus MV, Roix JJ, Sandklaeb A, Shields B, Sjogren M, Steinhoffsdottir V, Stringham HM, Swift AJ, Thorleifsson G, Thoersteinsdottir U, Timpson NJ, Tuomila T, Tuomilehto J, Walker M, Watanabe RM, Weedon MN, Willer CJ, Wellcome Trust Case Control Consortium. Identification of additional susceptibility loci for type 2 diabetes. Nat Genet 2008;40:638–645

8. Pihlajamaki J, Vanhala M, Vanhala P, Waterworth DM, Watkins N, Wellcome Trust Case Control Consortium. SNP and association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. Nat Genet 2008;40:638–645

9. Lagou V, Scott RA, Manios Y, Chen TL, Kiuva A, Pournimoula T, Moschonis G, Roma-Giannikou E, Pitsalidis YP. Impact of peroxisome proliferator-activated receptor γ and δ on adiposity in toddlers and preschoolers in the Generation R Study. Obesity (Silver Spring) 2009;17:1192–1198

10. Eriksson JG. The role of genes in growth and later health. Nestle Nutr Workshop Ser Pediatr cardiologe 2008;61:69–77

11. Meirhaeghe A, Boreham CA, Murray LJ, Tebbutt R, Wang G, Grammatikaki E, Kortuinen P, Kortuinen P, Vanono P, Marti A, Rey-Lopez JP, Phillips K, von Berlespach J, Sjoostrom M. Concurrent validity of a modified version of the International Physical Activity Questionnaire (IPAQ-A) in European adolescents: the HELENA Study. Int J Obes (Lond) 2008;32(Suppl. 5):S4–S11

12. Gauderman WJ, Morrison JM. QUANTO 1.1: a computer program for power and sample size calculations for genetic-epidemiology studies [article online]. Available from http://hydra.usc.edu/gxe. Accessed 17 November 2009

13. Barker DJ. Intrauterine programming of adult disease. Mol Med Today 1995;1:418–423

14. Horta BL, Bahl R, Martines JC, Victora CG. Evidence on the long-term effects of breastfeeding. Systematic reviews and meta-analyses. [article online]. Available from http://whqlibdoc.who.int/publications/2007/9789241195230_english.pdf. Accessed 17 November 2009

15. Harder T, Bergmann K, Raschschorn G, Pluhar P. Duration of breastfeeding and risk of overweight: a meta-analysis. Am J Epidemiol 2005;162:397–403

16. Memisoglu A, Hu FB, Hankinson SE, Manson JE, De Vivo I, Willett WC, Hunter DJ. Interaction between a peroxisome proliferator-activated receptor γ gene polymorphism and dietary fat intake in relation to body mass. Hum Mol Genet 2003;12:2923–2929

17. Luan J, Browne PO, Harding AH, Halsall DJ, O’Rahilly S, Chatterjee VK, Wareham NJ. Evidence for gene-nutrient interaction at the PPARγ locus. Diabetes 2001;50:686–689
Breast-feeding, BMI, and PPARG polymorphism

23. Carver JD. Advances in nutritional modifications of infant formulas. Am J Clin Nutr 2003;77:1550S–1554S

24. Laitinen K, Hoppu U, Hämäläinen M, Linderborg K, Moilanen E, Isolauri E. Breast milk fatty acids may link innate and adaptive immune regulation: analysis of soluble CD14, prostaglandin E₂, and fatty acids. Pediatr Res 2006; 59:723–727

25. Hollenberg AN, Susulic VS, Madura JP, Zhang B, Moller DE, Tontonoz P, Sarraf P, Spiegelman BM, Lowell BB. Functional antagonism between CCAAT/enhancer binding protein-α and peroxisome proliferator-activated receptor-γ on the leptin promoter. J Biol Chem 1997;272:5283–5290