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# A Birth-Season/DRD4 Gene Interaction Predicts Weight Gain and Obesity in Women with Seasonal Affective Disorder: A *Seasonal Thrifty Phenotype Hypothesis*

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We have recently described an association between the hypofunctional 7-repeat allele (7R) of the dopamine-4 receptor gene (DRD4), weight gain, and obesity in women with seasonal affective disorder (SAD). In the current study, we examined whether season-of-birth might interact with the 7R allele to influence body weight regulation in SAD. In 182 female probands with SAD, we performed an analysis of covariance predicting maximum lifetime body mass index (BMI) with both the exon-3 variable number of tandem repeat polymorphism of DRD4 and season-of-birth as independent variables, and age as the covariate. The overall model was highly significant ($F = 4.42$, $df = 8, 173$, $p < 0.0001$) with season-of-birth predicting maximal lifetime BMI both on its own and in its interaction with the 7R allele. The latter finding was attributable to 7-repeat carriers born in the spring ($N = 17$), who had a mean maximal lifetime BMI of 33.7 kg/m$^2$ (SD 8.6), compared to 26.7 kg/m$^2$ (SD 5.4) for all other probands combined ($N = 165$) ($F = 20.01$, $df = 1, 179$, $p < 0.0001$). The lifetime rate of obesity (maximal BMI $>30$ kg/m$^2$) was also significantly higher in the 7R/spring birth group (9/17 = 52.9% *vs* 32/165 = 19.4%; $\chi^2 = 9.94$, $df = 1$, $p = 0.002$; odds ratio = 4.68, 95% CI = 1.67–13.07). These data may reflect a novel gene–environment interaction, during early brain development, which establishes an increased risk for obesity in women with SAD. Although the mechanism for season-of-birth effects in psychiatric disorders is unknown, a characteristic pattern of melatonin exposure during the second and third trimesters may be of particular relevance in this study population. We speculate that these data may reflect the vestigial expression of a *seasonal thrifty phenotype* that contributed to the positive selection of the 7R allele over the past 40 000 years.
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## INTRODUCTION

### Atypical Symptoms of Depression and Obesity: Shared Genetic Vulnerability

Although a large body of knowledge has been generated on the biology of melancholic forms of depression characterized by loss of appetite, weight loss, and insomnia, much less is known about the biology of 'atypical' subtypes of depression defined by increased appetite, weight gain, and hypersomnia. A large study of 1029 female twin pairs using latent class analysis suggests that different genetic vulnerabilities might contribute to atypical *vs* melancholic forms of depression (Kendler *et al*, 1996), particularly as they relate to eating behavior and weight. In this study, twins with atypical depression weighed about 8 kg more than those with typical depression. Body mass indices (BMIs) and rates of bulimia were also substantially higher in the co-twins of those with atypical depression. This led the authors to hypothesize that 'familial/genetic factors that influence the vulnerability to atypical depression also influence the vulnerability to obesity'. Although this finding has significant implications for understanding the link between depressive disorders and obesity, there has been a dearth of subsequent research to elucidate the specific genetic mechanisms involved.

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### Atypical Depressive Symptoms, Seasonal Affective Disorder, and the Dopamine-4 Receptor Gene (DRD4)

Our group has examined a genetic model of atypical symptoms, weight gain, and obesity in women with seasonal affective disorder (SAD) based on DRD4. Most patients with SAD are premenopausal women who experience food cravings, weight gain, and hypersomnia in the fall–winter months, with full remission in the spring–summer period (Rosenthal *et al*, 1984). Prior authors have suggested that by conserving energy on a cyclical basis in anticipation of dwindling food supplies, these behavioral changes may be vestiges of an adaptive evolutionary process that historically conferred both individual survival (Rosenthal *et al*, 1987) and/or a reproductive advantage (Eagles, 2004; Davis and Levitan, 2005) in women of childbearing years. In modern developed countries with constant availability of high-caloric foods, this adaptation would become a risk factor for obesity in genetically prone individuals.

DRD4 is an excellent candidate for genetic association studies as it displays a high degree of variability, and a functional VNTR (variable number of tandem repeat) polymorphism has been identified in the third exon, the region coding for the third intracellular loop of the receptor (Van Tol *et al*, 1992). *In vitro* studies suggest that the exon III *DRD4 7-repeat* allele (7R) has decreased affinity for dopamine and transmits weaker intracellular signals in comparison to other exon III alleles (Asghari *et al*, 1995). This hypofunctionality is relevant to studies of obesity as weight gain has been associated with low brain dopamine activity (Comings and Blum, 2000; Wang *et al*, 2001; Volkow and Wise, 2005). Importantly, the D4 receptor is expressed in various brain regions that comprise the natural reward pathway (Civelli, 1995; Meador-Woodruff *et al*, 1996). Furthermore, primate studies have shown that reward expectancy related to food presentation is mediated by the prefrontal cortex (Watanabe, 1996), a brain area both rich in D4 receptors (Meador-Woodruff *et al*, 1996) and shown to mediate binge eating in both animal (Inoue *et al*, 1998) and human (Karhunen *et al*, 2000) studies. Treatment with the dopamine antagonist clozapine, which has high affinity for the D4 receptor (Van Tol *et al*, 1991), is often complicated by increased food consumption and weight gain, although the mechanism for this remains controversial (Bromel *et al*, 1998). An obese human homozygous for a D4 receptor null mutation has also been described (Nothen *et al*, 1994a). In support of the hypothesis that food reward mechanisms may be involved in these associations, a role for the 7R allele in mediating cue-elicited food craving has recently been found (Sobik *et al*, 2005).

In examining a possible role for DRD4 in SAD, we first reported a significant association between the hypofunctional 7R allele and maximum adult BMIs (Levitan *et al*, 2004a). In a subsequent report, we demonstrated that the link between the 7R allele and weight gain was strongly mediated by binge eating (Levitan *et al*, 2004b), further suggesting that altered brain mechanisms relevant to feeding behavior might be involved in this association.

### Season-of-Birth Effects

As reviewed by Torrey *et al* (1997), research into the effects of birth season on psychiatric illness dates back to the 1920s, and was based on the general hypothesis that seasonal changes in diet, vitamins, and/or sunlight would affect early brain development and thus later psychopathology (Tramer, 1929). By the 1960s, several large systematic studies were initiated, particularly in schizophrenic and manic-depressive psychosis, and before the turn of the millennium over 250 such studies had been completed in over 400 000 individuals. Of the 19 largest Northern Hemisphere studies on birth season and schizophrenia, all but one reported a statistically significant excess of winter–spring births compared to a group of matched controls. A similar pattern has been found in manic-depressive psychosis, although with less consistency across studies (Hare and Price, 1968; Dalén, 1975). Preliminary work in nonpsychotic bipolar disorder also points to a winter–spring birth excess (eg Torrey *et al*, 1996).

Surprisingly, only one published study has examined possible season-of-birth effects in SAD. In a large European study, Pjrek *et al* (2004) found an excess of spring–summer births in SAD patients compared to the general population. A highly novel finding, which has particular relevance to our own work, is that different season-of-birth effects were found depending on vegetative symptoms. Subjects with melancholic symptoms (which include loss of appetite and weight) were more often born in the fall/winter months, whereas atypical symptoms (which include overeating and weight gain) were associated with a spring/summer birth. Although they did not study appetitive symptoms separately, Pjrek *et al*'s data does suggest that factors tied to birth season might influence the early development of brain mechanisms relevant to eating behavior, weight, and SAD. The goal of the current study was to more directly examine whether season-of-birth effects might influence body weight regulation in SAD, including possible interaction effects with the 7R allele of DRD4.

## MATERIALS AND METHODS

### Sample

The current study sample consisted of 182 consecutive female outpatients, 18–65 years of age, who were presenting for a mood disorder consultation or responding to an ad, and met Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for major depression with a winter seasonal pattern. This extended sample included the probands described in our recent reports (Levitan *et al*, 2004a, b) as well as newly recruited probands. Subjects were recruited at the depression clinics of the Centre for Addiction and Mental Health (CAMH), Toronto, Ontario and the University of British Columbia (UBC) Hospital in Vancouver. Until recently, our genetic study has had a particular focus on women who overeat, and only those who experienced an increase in appetitive behavior and/or weight during their winter depressive episodes were included. The primary rationale for emphasizing this particular group was that carbohydrate craving and weight gain occur in over 70% of SAD patients, are particularly common in females, and are highly sensitive to bright light therapy (Rosenthal *et al*, 1984; Krauchi *et al*, 1993). Thus, increased appetitive symptoms constitute a core endophenotype in SAD. To limit the heterogeneity of

the current sample, five probands with a lifetime diagnosis of bulimia nervosa based on the Structured Clinical Interview for DSM-IV (SCID) interview (First *et al*, 2002) were excluded.

Each subject was given an oral and written summary of the purposes, procedures, and potential risks of the project, and gave informed written consent. The protocol was approved by the University of Toronto and University of British Columbia research ethics committees.

### Clinical Assessment

To assess major DSM diagnoses, each subject was administered the SCID (First *et al*, 2002) by a research assistant. To assess BMIs, each subject was also administered a brief questionnaire, which included a question about maximum weight achieved from age 16 onwards (excluding pregnancy), with corresponding height. BMIs were calculated for each subject using the formula (weight in kilograms/(corresponding height in meters)$^2$).

### Laboratory Methods

Blood samples were sent to the Centre for Addiction and Mental Health neurogenetics laboratory. Genomic DNA was extracted from white blood cells using the high-salt method. All genotyping of the DNA was performed blind to psychiatric diagnosis, and *vice versa*. This was facilitated through a standard patient identification coding system employed by our laboratory. The 48 bp VNTR region in the third exon of *DRD4* was amplified using polymerase chain reaction (PCR) techniques with primers and conditions published previously (Lichter *et al*, 1993). The PCR products were visualized via gel electrophoresis performed in 3.5% agarose prepared with ethidium bromide and 1 × TBE (Tris, boric acid, ethylenediaminetetraacetic acid).

### Statistical Methods

Two genotypic groups were defined based on whether probands did or did not carry at least one copy of the hypofunctional 7R allele of DRD4 (designated the 7R and no7R groups, respectively). Four season-of-birth groups were also defined, with groupings based on the calendar year (ie probands with a spring birth were born between March 22 and June 21 inclusive, summer births were between June 22 and September 21 inclusive, fall births between September 22 and December 21 inclusive and winter births between December 22 and March 21 inclusive). The genotype × birth season interaction thus included eight groups, including four with the 7R allele (7R/spring, 7R/summer, 7R/fall, and 7R/winter) and four without this allele (no7R/spring, no7R/summer, no7R/fall, and no7R/winter).

A 2 (genotype) × 4 (season-of-birth) analysis of covariance (ANCOVA) was carried out with maximum lifetime BMI as the dependent variable and age as the covariate. *Post hoc* analyses employed the least significant difference test to assess which particular subgroups differed significantly from one another. As inclusion of a covariate precludes the use of *post hoc* tests to examine pairwise group differences, age was removed from these analyses.

In order to best align our data with the obesity literature, we also performed a selected analysis based on categorical definitions of obesity (maximal BMI > 30 kg/m$^2$) and morbid obesity (maximal BMI > 40 kg/m$^2$) using Pearson's $\chi^2$ test.

Finally, to assess whether population stratification based on ethnicity was contributing to our results, we retested our statistical model in the subsample of probands of Caucasian ancestry.

The significance level for the overall ANCOVA was set at $p < 0.01$. Given the large number of study groups, which limits statistical power, a significance level of 0.05 was set for the main and interaction effects, *post hoc* tests, and $\chi^2$ analyses.

## RESULTS

### Sample Characteristics

The mean age of the sample was 38.3 ± 9.5 years. Ancestral information was available for 170 probands, of whom 157 (92.4%) were Caucasian, three (1.8%) Caribbean or African American, two (1.2%) Oriental, one (0.6%) Native Canadian Indian, and seven (4.1%) of mixed ancestry. The frequency of the common 4-repeat and 7R alleles was 70.3% and 18.1%, respectively, highly consistent with prior studies. There was no deviation from Hardy–Weinberg equilibrium. There were 63 probands (34.6%) with at least one version of the 7R allele. There was no significant difference in age between the two genotypic groups defined by the presence or absence of the 7R allele, or in the four groups defined by birth season.

### Maximal BMI, DRD4, and Season-of-Birth

All BMI measures are in kg/m$^2$. The mean maximal BMI for the entire sample was 27.4 ± 6.1. Corresponding values for carriers and noncarriers of the 7R allele were 28.8 ± 7.0 and 26.6 ± 5.4, respectively. The mean maximal BMIs based on birth-season groupings were: spring 29.4 ± 8.1 ($N = 49$); summer 26.4 ± 5.0 ($N = 38$); fall 26.3 ± 4.1 ($N = 46$); and winter 27.2 ± 5.7 ($N = 49$).

The ANCOVA results predicting maximal BMI are summarized in Table 1. The overall model was highly significant ($p < 0.0001$), accounting for 17.0% of the variance in maximal lifetime BMI in this sample. As shown, the two main effects and the genotype × birth season interaction were all statistically significant.

### *Post hoc* Testing of the DRD4/Birth Season Interaction

Figure 1 summarizes the mean maximal BMI in the eight subgroups defined by the interaction of DRD4 genotype (7R present or absent) and season-of-birth (spring, summer, fall, and winter). *Post hoc* testing revealed that all of the significant pairwise group differences for this interaction were attributable to the high mean maximal BMI in 7R carriers who were born in the spring (ie the 7R/spring birth group). As indicated, this group had a significantly higher mean maximal lifetime BMI than each of the other interaction groups at $p < 0.001$, except for the 7R/fall birth group, which differed at $p < 0.01$. None of the other seven interaction groups differed significantly from

**Table 1** ANCOVA Predicting Maximum Lifetime Body Mass with DRD4 Genotype and Birth Season, Covaried by Age, in 182 Women with Seasonal Affective Disorder

| | df | F | *p*-value | Partial $\eta^2$ | Power |
|---|---|---|---|---|---|
| Overall model | 8 | 4.42 | <0.0001 | 0.170 | 0.995 |
| *Variable* | | | | | |
| Age | 1 | 8.97 | 0.003 | 0.049 | 0.846 |
| DRD4 genotype[a] | 1 | 4.62 | 0.033 | 0.026 | 0.570 |
| Birth season[b] | 3 | 3.89 | 0.01 | 0.063 | 0.819 |
| DRD4 × birth season | 3 | 3.24 | 0.024 | 0.053 | 0.737 |
| Error | 173 | | | | |
| Total | 182 | | | | |

df, degrees of freedom.
[a]Genotype defined by the presence or absence of the 7-repeat allele of DRD4.
[b]Spring = March 22–June 21; Summer = June 22–September 21; Fall = September 22–December 21; Winter = December 22–March 21.

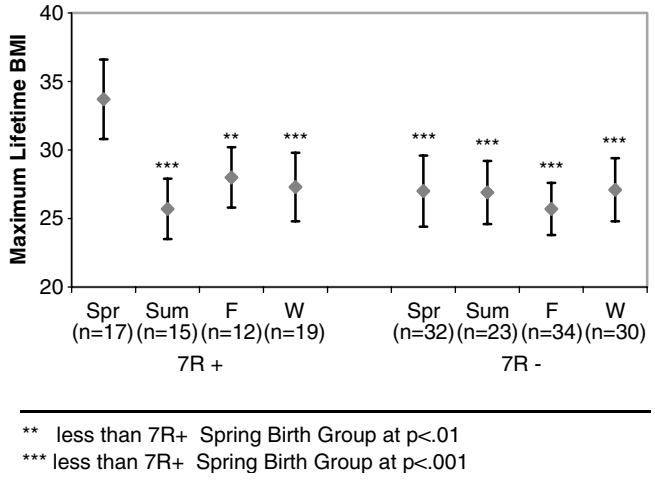


**Figure 1** Mean maximal lifetime BMI (±SEM) in the eight groups defined by the interaction of DRD4 genotype (7R present/absent) and birth season in 182 women with SAD. **Less than 7R + spring birth group at $p<0.01$. ***Less than 7R + spring birth group at $p<0.001$.

one another. Based on these results, and for the purposes of replication studies, the 7R/spring birth group ($N=17$) was designated the 'high-risk' group, whereas other probands were collapsed into a single 'low-risk' group ($N=165$). The mean maximal BMI in these two groups were 33.7±8.6 and 26.7±5.4, respectively ($F=20.01$, $df=1,179$, $p<0.0001$; age covaried).

### Rates of Obesity and Morbid Obesity

Lifetime rates of obesity and morbid obesity were next compared in the 'high-risk' and 'low-risk' groups using Pearson's $\chi^2$. The corresponding rates of obesity were as follows: 7R/spring birth group—9/17 = 52.9% *vs* low-risk group—32/165 = 19.4%, $\chi^2=9.94$, $df=1$; $p=0.002$; odds ratio = 4.68, 95% CI = 1.67–13.07). The rates of morbid obesity were also significantly greater in the 7R/spring birth group (4/17 = 23.5% *vs* 6/165 = 3.6%; $\chi^2=11.75$, $df=1$, $p<0.001$; odds ratio = 8.15, 95% CI = 2.04–32.60).

### Analysis of Caucasian Probands

In the subsample of 157 probands of Caucasian ancestry, the ANCOVA predicting maximal BMI showed that the main effects of genotype and birth season, and the genotype × birth season interaction, all remained statistically significant. In these Caucasian probands, the mean maximal BMI in the 'high-' and 'low-risk' groups defined above were 34.5±9.0 and 26.8±5.5, respectively ($F=19.13$, $df=1,156$, $p<0.0001$). This suggests that population stratification of the 7R allele across ethnic groups was not a major contributor to the overall results.

## DISCUSSION

The current results extend our genetic model of weight gain and obesity in women with SAD by suggesting that birth-season interacts with the DRD4 gene to influence body weight regulation in this population. Female SAD probands having the combination of both a 7R allele and spring birth had a mean maximal BMI 26.2% greater than reported by other probands. Furthermore, among the eight interaction groups defined by genotype and birth season, all pairwise group differences were attributable to the 7R/spring birth group. Pending replication in other samples, these data may reflect a novel gene–environment interaction during early brain development, which establishes an increased risk for obesity in women with SAD.

In demonstrating a possible gene–environment interaction in early development that promotes weight gain and obesity later in life, the current results are highly reminiscent of the *thrifty phenotype hypothesis* (TPH) of Hales and Barker (2001). This hypothesis was developed to explain observed associations between low birth weights, impaired glucose tolerance, and the metabolic syndrome (Hales *et al*, 1991). As discussed by these authors, a low birth weight and long-term insulin resistance are adaptive for a developing organism if food supplies are scarce and likely to remain so over a sustained period. They propose that a thrifty phenotype is triggered by one or more signals of maternal malnutrition passing across the placenta to the developing fetus, essentially providing the fetus with a forecast of an impoverished nutritional environment into which it will be born. If the prediction proves wrong, however, and food supplies become abundant, the thrifty phenotype is maladaptive, becoming a risk factor for diabetes, obesity, and related disorders. Thus, the key elements of a thrifty phenotype are as follows: (1) the primary function is conservation of energy, (2) it is anticipatory in nature, based on a prediction of limited future food resources, (3) it is set into motion in early development by signals passing from mother to fetus, and (4) it becomes maladaptive in an ample food environment.

We propose that the current findings related to obesity, season-of-birth, and the DRD4 gene may reflect a novel *seasonal thrifty phenotype* (STP) that incorporates each of the four characteristics outlined above, although in a slightly different way. To help illustrate this, Table 2 compares our model to the TPH described by Hales and Barker (2001).

The most important feature of both the TPH and putative STP is the prediction of, and adaptation to, an environment

**Table 2** Core Features of the *Thrifty Phenotype* (Hales and Barker, 2001) and Proposed *Seasonal Thrifty Phenotype* (STP)

| | ***Thrifty phenotype* (Hales and Barker)** | ***Seasonal Thrifty Phenotype* (Levitan *et al*)** |
|---|---|---|
| Adaptation to/prediction of | Long-term, episodic famine | Predictable seasonal famine |
| Physiological adaptation | Metabolic (low insulin secretion; insulin resistance) | Behavioral (seasonal food cravings, increased eating, decreased activity, hypersomnia) |
| Phenotype | Type II diabetes, obesity | SAD with reversed vegetative symptoms, marked weight gain/obesity |
| *In utero* signal | Of maternal malnutrition | of latitude (via maternal melatonin pattern) |
| Maladaptive in | Plentiful food environment | Plentiful food environment |

with limited food resources. In the TPH, the adaptation and prediction relate to episodic and prolonged famines that might continue over the entire lifespan of the organism. In the STP, the prediction is for reliable seasonal famines intermittent with periods of increased food resources, which is more likely to occur at latitudes far from the equator. Whereas energy conservation is the goal in both cases, the process that best enables this differs in each case. In the TPH, a decreased long-term capacity for insulin secretion and insulin resistance are the primary mechanisms, whereas the STP is based on energy conservation through more easily reversible behavioral changes such as overeating, hypersomnia, and fatigue—the 'atypical' or 'reversed' vegetative symptoms of depression that are highly characteristic of SAD. The corresponding phenotypes are diabetes/obesity for the TPH and SAD with reversed vegetative features associated with marked weight gain/obesity in the STP.

Both thrifty phenotypes rely on a signal from mother to fetus that makes a prediction about long-term food resources. Whereas the original thrifty phenotype is triggered by one or more signals of maternal malnutrition, in the STP, the corresponding signal must have information relevant to seasonality. One way this could occur is via a distinct melatonin signal from mother to fetus during a critical period in gestation. In animals, maternal melatonin readily crosses the placenta and enters the fetal circulation, providing photoperiodic information that influences both circadian and seasonal rhythms in the offspring (Thomas *et al*, 1998). Of potential relevance to the DRD4 gene, melatonin–dopamine interactions may also contribute to seasonal rhythmicity in animals (Zisapel, 2001). Although it is unknown whether this same process occurs in present-day humans, the anatomical, molecular, and functional substrates of such mechanisms have been well conserved in our species (Wehr, 2001). A specific interaction between photoperiod, the melatonin–dopamine system, and the subsensitive 7R allele of DRD4 has also been proposed (Seeger *et al*, 2004).

How might a spring birth be relevant to our model? One speculation is that for the STP to be triggered, fetal exposure to a fall/winter melatonin pattern must occur at a critical point of brain development in the second or third trimesters. This unique melatonin pattern may be necessary to sensitize the developing fetus to this same photoperiodic signal later in life. Preclinical studies to examine seasonal weight gain in adulthood, based on controlled photoperiodic exposures during late gestation, would be of great interest in this regard.

## The 7R Allele of DRD4 as a Seasonal Thrifty *Genotype*

The current data may also have direct relevance to evolutionary models of the DRD4 gene. There is now significant evidence that the 7R allele in particular started off as a rare mutational event, and has been strongly positively selected for in various human populations over the past 40 000 years (Ding *et al*, 2002). We have previously suggested that the ability of young women to conserve body mass in the fall and winter months, mediated by an effect of the 7R allele on eating behavior, might have been a factor in this positive selection process (Levitan *et al*, 2004b). The current results further suggest that the 7R allele could play a role in a type of early developmental plasticity that matches adult feeding and activity patterns to predicted seasonal famines. At some point in human evolution, the ability to anticipate rather than simply react to seasonal food shortages might have conferred a survival and/or reproductive advantage on its own (Davis and Levitan, 2005). In this way, the early gene–environment interaction suggested by the current data may in itself have contributed to the positive selection of the 7R allele over time.

## Limitations and Future Directions

To refine our *seasonal thrifty phenotype hypothesis* going forward, more work is needed to fully characterize the phenotypic differences between the high- and low-risk groups identified in the current analysis. Whereas the model we propose assumes that the weight gain observed in our high-risk probands is seasonal in nature and based on reversed vegetative symptoms in some way, large-scale prospective studies will be needed to demonstrate this empirically. A possible role for metabolic factors cannot be ruled out at this time. It will also be important to demonstrate that similar season-of-birth/DRD4 interactions do not occur in nonseasonal obese populations. One prior study of DRD4 in a heterogenous obese population was in fact negative (Hinney *et al*, 1999), although season-of-birth effects were not part of this work. Another prediction of our model that was not testable in the current data set is that only pregnancies carried at relatively extreme latitudes will demonstrate the observed effect. The model should not apply to individuals born near the equator, and for individuals born in the southern hemisphere, one might expect season-of-birth effects related to the corresponding spring period of September to December.

In summary, the current results point to a novel gene–environment interaction during early brain development,

which establishes an increased risk for obesity in women with SAD. These data may reflect the vestigial expression of an STH that contributed to the positive selection of the 7R allele over the past 40 000 years.

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