A Mathematical Model for Predicting Obesity Transmission with Both Genetic and Nongenetic Heredity

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Objective: Obesity is transmissible across generations through both genetic and nongenetic routes, but distinguishing between these factors is challenging. This study aimed to quantitatively examine the contribution of these genetic and nongenetic effects to assess their influence on obesity prevalence.

Methods: A mathematical model was proposed that incorporated both the genetic and nongenetic effects of obesity. Model parameters were estimated by using observational data. Model simulations were used to assess the sensitivity of model parameters. To strengthen the study’s approach, parameter estimation and simulation using data from the United Kingdom were also performed.

Results: Individuals homozygous for a “hypothetical obesogenic gene” were suggested to be more susceptible to both socially contagious risk and spontaneous weight gain risk. The model predicted that obesity prevalence would reach 41.03% (39.28, 44.31) and 26.77% (25.62, 28.06) at 2030 in the United States and United Kingdom, respectively. The socially contagious risk factor had a greater overall impact on the distribution of the population with obesity than did spontaneous weight gain risk or mother-to-child obesity transmission risk.

Conclusions: Although the proposed “first approximation” model captured the complex interactions between the genetic and nongenetic effects on obesity, this framework remains incomplete. Future work should incorporate other key features driving the obesity epidemic.

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Introduction

Obesity prevalence has increased steadily for the past few decades. Although obesity is considered to be a noncommunicable disease, evidence of the contagiousness of obesity has accumulated in the past 10 years. In 2007, Christakis and Fowler introduced a modeling framework that studied the impact of social influences on obesity, whereby individuals with more contact with other persons with obesity have a higher risk of developing obesity (1). Although the analytical methods have been debated (2), Christakis and Fowler reported that the association between weight gain risk and the connection with other persons with obesity remains even after the removal of other possible confounders, including common environmental factors. Thus, they concluded that obesity is contagious through social connections. The complete mechanism behind the social contagion of obesity has not been fully elucidated, but scientific evidence for social contagion is accumulating. For example, it was recently found that adolescents tend to have more friends with similar physical activity levels and eating behaviors (3,4).

Obesity is also transmitted vertically from parents to offspring through or beyond genome sequences (intergenerational transmission) (5). Heredity studies have found that a substantial proportion (60%-80%) of the variance in BMI distribution can be explained by genetic variance (6,7). Genome-wide association studies have identified multiple genes and single-nucleotide polymorphisms that affect obesity (8,9). Among them, the fat mass and obesity-associated gene (FTO) is strongly associated with increased BMI, although the detailed mechanism behind this association is not clear (10). Interestingly, however, the FTO genotype is not associated with outcomes after weight loss interventions (11). Vertical transmission also results from the fetal
environmen by the parental, especially maternal, lifestyle (12). Maternal obesity has an epigenetic impact on the expression of metabolic genes in children, a finding that has been experimentally documented in mice (13). Furthermore, maternal obesity (and maternal diet during pregnancy and lactation) interrupts the construction of neural circuits in the hypothalamus, which regulate the offspring’s appetite and which may influence a path toward obesity later in adulthood (14). Also, maternal diet during pregnancy and lactation impacts children’s growth (15). Taken together, the data suggest that even after excluding genetic factors, children of mothers with obesity are at higher risk of obesity themselves.

Despite the evidence of intergenerational obesity transmission, quantification of the influence of intergenerational obesity transmission on obesity prevalence remains elusive. There are two significant challenges to quantifying this influence. First, estimating relative risk requires carefully designed, large-scale surveillance, which is difficult to conduct in a wide-reaching population. Qi et al. estimated the relative risk of the FTO gene using two large cohort studies (the Nurses’ Health Study and the Health Professionals Follow-Up Study), but their analysis was confined to specific populations and may not represent national population trends (16). Second, the interdependency of the different sources of obesity risk is impossible to measure directly and separately. For example, the genetic correlation between direct genetic effect and maternal effects makes it hard to observe both effects separately. A mother carrying “obesity genes” may pass these genes to her offspring (direct gene effect) and is susceptible to developing obesity herself, which increases her child’s childhood obesity risk (phenotypic transmission).

Mathematical models can account for these interdependencies and allow investigators to hypothesize different scenarios by changing parameters. Because the dynamics of obesity resemble the dynamics of a contagious infectious disease, several investigators have proposed obesity prevalence models based on the Kermack-McKendrick infectious disease model (17). Previous dynamic obesity prevalence models have incorporated both social and nonsocial influences on obesity (18–21), and Hong et al. additionally incorporated genetic heredity (22). Dawson et al. proposed a statistically based computational model that accounted for assortative mating and fertility rate differentiated by BMI that reflects the transient BMI distribution across generations (23).

Advancing previous approaches, here we construct a mathematical model in which we included both genetic and nongenetic effects. To demonstrate the usefulness of the model, we applied the model to address two key questions: (1) How much do genetic characteristics contribute to obesity prevalence? and (2) How do interventions that target social influences, nonsocial influences, and pregnancy-related influences on obesity risk impact trends in obesity prevalence?

### Methods

#### Models for the obesity epidemic

Following the approach derived from infectious disease modeling (24), we compartmentalized the population into two subgroups by phenotype: a class without obesity (underweight, normal, and overweight; BMI < 30 kg/m²), termed S, and a class with obesity (BMI ≥ 30 kg/m²), termed I. These classes were further divided into three subgroups by the genotype of a hypothetical obeseogenic gene: AA, Aa, and aa. Thus, for example, $S_a$ is the proportion of the population without obesity with the $Aa$ genotype. We adopted Mendelian laws of genetic heredity. To present the simplest model that reflects reality, we did not consider continuous BMI values and other physiological and socioeconomic features. All time-dependent variables in the model and their descriptions are shown in Table 1. The proportion of the population determined by genotype ($N_i$, where $i, j \in \{A, a\}$) is the sum of proportion of populations with and without obesity with the same genotype (i.e., $N_{ij} = S_{ij} + I_{ij}$). The allele frequencies for $A$ and $a$, $c_A$ and $c_a$, are described by $N_i$ as follows: $c_A = N_{AA} + \frac{N_{Aa}}{2}$, $c_a = N_{aa} + \frac{N_{Aa}}{2}$ because the gene from homozygous ($AA$ or $aa$) individuals is $A$ or $a$ with a 100% chance but the gene from heterozygous ($Aa$) individuals is $A$ with a 50% chance or $a$ with a 50% chance. Here, we describe the most important characteristics of the model; a comprehensive description is included in the Supporting Information.

1. **Birth process.** The natural birth rate is denoted by $v$. Newborn genotype is formulated by combining maternal and paternal genotype; the maternal (and paternal) gamete receives one of the paired alleles. Assuming random mating, the proportion of newborns with a specific genotype is determined by the allele frequencies: the proportions of newborns with genotype $aa$, $AA$, and $Aa$ are $c_a^2$, $c_A^2$, and $2c_Ac_a$, respectively. The childhood obesity risk is differentiated by the maternal phenotype; the risk given that the mother does not have obesity is $k_1$; if the mother has obesity, the risk is $k_2$. The maternal phenotype (obesity or nonobesity) affects the phenotype of children, regardless of maternal genotype. This is called “phenotypic (nongenetic) transmission.”

2. **Obesity flow rates.** All individuals without obesity are at risk of developing obesity after birth. We assumed progression to obesity with two terms: “socially contagious weight gain risk” and “spontaneous weight gain risk.” To model potential social draws to obesity, we applied a first-order term that is linearly dependent on the proportion of obesity among total population $\beta_g$ is the coefficient for the rate of obesity.

| Variable | Description |
|----------|-------------|
| $S_{aa}$ | Proportion of population without obesity with no risk allele (genotype: $aa$) |
| $S_{Aa}$ | Proportion of population without obesity with one risk allele (genotype: $Aa$) |
| $S_{AA}$ | Proportion of population without obesity with two risk alleles (genotype: $AA$) |
| $I_{aa}$ | Proportion of population with obesity with no risk allele (genotype: $aa$) |
| $I_{Aa}$ | Proportion of population with obesity with one risk allele (genotype: $Aa$) |
| $I_{AA}$ | Proportion of population with obesity with two risk alleles (genotype: $AA$) |
| $N_{aa}$ | Proportion of population with no risk allele (genotype: $aa$) |
| $N_{Aa}$ | Proportion of population with one risk allele (genotype: $Aa$) |
| $N_{AA}$ | Proportion of population with two risk alleles (genotype: $AA$) |
| $c_A$ | Frequency of allele $A$ among total population |
| $c_a$ | Frequency of allele $a$ among total population |
Assessment of different interventions to predict future obesity prevalence

We may be able to estimate the genetic and nongenetic effects on obesity development by conventional simulation methods in genetics, such as SIMLA, MERLIN, and PLINK (32). However, the advantage of employing a mathematical model instead of conventional methods is that it enables us to project future obesity prevalence scenarios simply by changing parameters or initial conditions. Hereafter, after setting the estimated values of the parameters at baseline (Table 2), we investigated (1) how much the hypothetical obesogenic gene contributes to obesity prevalence and (2) how intervention programs influence future obesity prevalence. The obesity prevalence changes dynamically at first but reaches a specific value (which is determined by the set of parameters) as time goes by, and we observed this “converged prevalence” or plateau to compare different scenarios. We used the best-fit parameters as baseline.

1. Genetic effect of a hypothetical obesogenic gene. In our model, the genetic effect is on the susceptibility to obesity due to socially contagious risk, $\beta$, and that due to spontaneous weight gain risk, $\eta$, and both of the parameters differ by genotype. To investigate the population-level impact of those genetic effects, we observed that simulations as the estimated values of $\beta_{AA}, \eta_{AA}$ are moved toward the estimated values of $\beta_{AA} (= \beta_{aa}), \eta_{AA} (= \eta_{aa})$.

2. Impact of obesity intervention programs. We created the above scenario to elucidate the genetic effect of a hypothetical obesogenic gene by varying parameters for individuals who possessed the hypothetical obesogenic gene. However, given that interventions to control weight usually target the whole population or are customized for individuals with specific phenotypes or demographics (obesity, nonobesity, pregnant, race/ethnicity, sex, etc.) regardless of genotype, it may be more helpful to assess the impact of obesity intervention programs targeting the whole population or populations with a specific phenotype. In this study, we define “implementing intervention programs” as changing parameters. We assessed the impact of the following scenarios: (a) impeding social contagion for whole population, (b) impeding spontaneous weight gain for whole population, and (c)
managing gestational weight gain for pregnant women with obesity. (a) or (b) corresponds to reducing $\beta$ or $\eta$ of the whole population at the same time, and (c) corresponds to reducing $k_2$. The above analysis for the assessment of intervention programs was carried out only for the case of the United States. We used the statistical computing software R 3.3.1 (The R Foundation for Statistical Computing) and its library “deSolve” for simulation.

### Results

#### Interpretation of the numerical predictions

Before formalizing and quantifying model results, we emphasize that the model represents a “first approximation,” which incorporated several key components that are considered to be potentially important drivers of the obesity epidemic. Because we may be missing other components and drivers of the obesity epidemic, we caution that the predictions should be interpreted with the model assumptions, which we revisit in the Discussion section.

#### Estimated parameters and predicted obesity prevalence

The best-fit parameters are shown in Table 2. The coefficient for the transition rate due to socially contagious weight gain risk ($\beta$) and the transition rate due to spontaneous weight gain risk ($\eta$) for the individuals with genotype $aa$ and $Aa$, respectively, was estimated from 0.0000 to 0.0122 and 0.0027 to 0.0046, respectively. The coefficient for the transition rate due to socially contagious weight gain risk for the individuals with genotype $AA$ and $Aa$ was estimated from 0.1901 to 0.1838 and 0.4954 to 0.0046, respectively. The transition rate due to spontaneous weight gain risk for the individuals with genotype $aa$ and $Aa$ was estimated from 0.0002 to 0.0027 and 0.0117 to 0.0046, respectively. The death rate $\mu$ was estimated from 0.0000 to 0.0123, assumed to be same as birth rate.

The obesity prevalence trajectory is shown in Figure 2A and Figure 3. At first, obesity prevalence continuously increases and reaches 41.03% (95% CI: 39.28-44.31) and 26.77% (95% CI: 25.62-28.06) at 2030 in the United States and United Kingdom. As time evolves, further obesity prevalence gradually reaches a stable state at 52.77% (95% CI: 48.69-58.30) and 26.84% (95% CI: 22.22-32.62) in the United States and United Kingdom, respectively. We can observe that the model tracks the obesity prevalence after the period used for estimation (open circles in Figure 2A and Figure 3). Interestingly, the prevalence converges earlier in the United Kingdom than in the United States. Figure 2B shows the genotype distribution trajectory, which appears nearly stable during the time period of simulation. Repeated numerical simulations confirmed that the initial obesity prevalence does not alter the converged obesity prevalence; the initial genotype distribution, however, substantially alters it.

Supporting Information Figure S4 shows the percentage of new cases (incidences) of obesity due to the socially contagious risk factor among people who develop obesity at time $t$. $p(t)$ in the United States. The number of individuals who develop obesity at time $t$ is $(\beta_{AA}(t)+\eta_{AA})S_{AA}+(\beta_{Aa}(t)+\eta_{Aa})S_{Aa}+(\beta_{aa}(t)+\eta_{aa})S_{aa}$, and those who develop obesity due to contagious risk is $\beta_{AA}(t)S_{AA}+\beta_{Aa}(t)S_{Aa}+\beta_{aa}(t)S_{aa}$, which leads to $p(t) = \frac{\beta_{AA}(t)S_{AA}+\beta_{Aa}(t)S_{Aa}+\beta_{aa}(t)S_{aa}}{(\beta_{AA}(t)+\eta_{AA})S_{AA}+(\beta_{Aa}(t)+\eta_{Aa})S_{Aa}+(\beta_{aa}(t)+\eta_{aa})S_{aa}}$. $p(t)$ increases as the contagious risk (in other words, the population with obesity) increases. During the course of the epidemic, about 75% of the population develops obesity due to the contagious risk.

#### Genetic effect

To see the population-level impact of the hypothetical obesogenic gene, we simulated the model varying $\beta_{AA}$ from 0.184 (baseline) to 0.012,
which is equal to the estimated value of $\beta_{AA} (\beta_{Aa})$ (Figure 4A). When $\beta_{AA}$ was reduced to 0.012, the converged prevalence fell to 40.35%. Similarly, we varied $g_{AA}$ from the baseline (0.0046) to the level of $g_{Aa}$ (0.0027) and observed the converged obesity prevalence (Figure 4B). In this case, the prevalence slightly decreased, but the impact was quite small compared with socially contagious risk. The converged obesity prevalence reached 52.71% as $\eta_{AA}$ reached the level of $\eta_{Aa}$.

Impact of obesity intervention programs

To see the impact of different obesity intervention programs, we compared the converged obesity prevalence by relatively changing the parameters: the coefficient for the transition rate due to the socially contagious weight gain risk ($\beta$), the transition rate due to the spontaneous weight gain risk ($g$), and the phenotypic transmission risk ($k^2$) in the United States. Figure 5 shows the obesity prevalence when we magnified (or reduced) each obesity risk for all genotypes simultaneously, where 1 (relative change) corresponds to the estimated level of each risk. We found that the relative change in the socially contagious weight gain risk modifies the converged obesity prevalence more than changing the other risk. For example, if we reduce the transition rate due to socially contagious weight gain risk to the 50% level of the baseline value, the prevalence reaches 39.60% as time goes to infinity. Meanwhile, even if the transition rate due to spontaneous weight gain risk, $g$, is reduced to the 50% level of the baseline, it can reach 48.00%. The effect of the intervention against the phenotypic transmission risk, $k$, is also quite limited (48.94%).

Discussion

Our model describes the time evolution of obesity prevalence and the prevalence of a hypothetical obesogenic gene accounting for phenotypic and genetic heredity. When we combined empirical data with our proposed model, we found a difference in socially contagious weight gain risk and spontaneous weight gain risk between homozygotes and others, which suggests that individuals with the homozygous genotype of the hypothetical obesogenic gene are more susceptible to obesity. The simulation suggested that the genetic factor is important because it modifies susceptibility to socially contagious weight gain risk. Furthermore, we found that reducing the socially contagious risk factor had the biggest impact on obesity prevalence.
Although some of our results are readily applied, we again emphasize that given both the reasonable and controversial (meaning we cannot judge reasonability at this stage) assumptions used to simplify the model as listed in Supporting Information Table S1, the results should not be interpreted without considering those assumptions. We have to be especially careful in interpreting the effect of “intervention” programs. Although the model can be used to provide insight into hypothetical questions regarding, for example, the impact of policy decisions, these conclusions should be balanced against the model assumptions. Relaxing or changing these assumptions may lead to different conclusions.

Our model contains several strong assumptions. For example, we didn’t consider paternal effect. Despite this, maternal obesity may have a stronger influence on infant obesity (33) for both biological and sociological reasons: the prenatal (intrauterine) environment is a risk factor for chronic disease including obesity, and the mother-child relationship in nutrition intake is stronger than between father and child (34). Another assumption we did not consider is other social factors or age-dependency that can affect spontaneous weight gain risk. Moreover, all of the parameters were fixed over time. We made these stronger yet reasonable assumptions to keep the model simple and tractable, given the trade-off between complexity and tractability of mathematical models. However, incorporating these additional factors into the mathematical model is a future aim of our work.

We are not the first to model the genetic effect of obesity. Hong et al. incorporated the role of genetic effects in a mathematical model and investigated these effects on obesity prevalence (22). This study assumed that the mortality rate of individuals with obesity was higher than that of normal-weight individuals and that the obesity risk is the socially contagious risk only, which led them to conclude that the population with the hypothetical obesogenic gene variant (AA or Aa) would continue to decrease in the long run (1,000 years later) and that “the effect of environmental factors on the dynamics of obesity are negligible.” Hence, this is a good demonstration that results can differ depending on the model assumptions and study purpose.

There remains a plausibility problem regarding modeling assumptions; however, the strength of our model is that we can correct the model based on different assumptions. For example, phenotypic transmission is not uniformly supported by all recent large-scale cohort studies (35-37). Thus, readers using the model who do not think the assumption of
phenotypic transmission is acceptable can realize this in the model by simply assuming $\beta_a=0$. Also, if the assumption that spontaneous weight gain risk is time constant is not acceptable (we fixed the parameter over time because we don’t know how it changes in the future), the reader can use a time-dependent function for spontaneous weight gain risk. Furthermore, it is still not well known how the FTO gene works on social behavior. This is the reason we set different parameters for the socially contagious risk of different genotypes ($\beta_{aa}=\beta_{ab} \neq \beta_{bb}$). If readers do not agree with this assumption, they can realize their assumption simply by setting $\beta_{aa}=\beta_{ab}=\beta_{bb}$.

Despite these disadvantages that are mainly relevant to model assumptions, we note several advantages of our study. First, this is the first study proposing an obesity prevalence model that accounts for both phenotypic and genetic obesity heredity and socially contagious risk in a single model. This enabled us to compare the impacts of different types of risk factors. Second, compared with conventional epidemiologic studies, we modeled the time course of the obesity epidemic, which enabled us to predict future obesity prevalence.

We have refined the mathematical framework incorporating the genetic heredity of obesity. The model assumptions in Supporting Information Table S1 are oversimplified and are in no way intended to undermine the complexity of the obesity prevalence or to undermine prior studies and findings. Those findings are helpful for constructing the more valid obesity epidemic model, which will be used in predicting obesity prevalence and understanding the current and future epidemic in the United States and worldwide.

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References

1. Christakis NA, Fowler JH. The spread of obesity in a large social network over 32 years. N Engl J Med 2007;357:370-379.
2. Lyons R. The spread of evidence-poor medicine via flawed social-network analysis. Stat Politics Policy 2011;2:21. doi:10.2202/2151-7509.1024
3. Schofield L, Mummery WK, Schofield G, Hopkins W. The association of objectively determined physical activity behavior among adolescent female friends. Res Q Exerc Sport 2007;78:9-15.
4. Voorhees CC, Murray D, Welk G, et al. The role of peer social network factors and physical activity in adolescent girls. Am J Health Behav 2005;29:183-190.
5. Whisner RC, Wright JA, Pepe MS, Snedel KD, Dietz WH. Predicting obesity in young adulthood from childhood and parental obesity. N Engl J Med 1997;337:869-873.
6. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet 1997;27:325-351.
7. Nan C, Guo B, Warner C, et al. Heritability of body mass index in pre-adolescence, young adulthood and late adulthood. Eur J Epidemiol 2012;27:247-253.
8. Thorellson G, Walters GB, Gudbjartsson DF, et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. Nat Genet 2009;41:18-24.
9. Loos RJ, Lindgren CM, Li S, et al. Common variants near MC4R are associated with fat mass, weight and risk of obesity. Nat Genet 2008;40:768-775.
10. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007;316:889-894.
11. Livingstone KM, Celso-Morales C, Papadonatos GD, et al. FTO genotype and weight loss: systematic review and meta-analysis of 9563 individual participant data from eight randomised controlled trials. BMJ 2016;354:i4707. doi:10.1136/bmj.i4707
12. Patti ME. Intergenerational programming of metabolic disease: evidence from human populations and experimental animal models. Cell Mol Life Sci 2013;70:1597-1608.
13. Zhai Y, Sulayman X, Li WR, Shen C, Zhao WH, Shi XM. The relationship between socioeconomic status and overweight and obesity among elementary school children in China [in Chinese]. Zhonghua Yu Fang Yi Xue Za Zhi 2013;47:945-948.
14. Morris MJ, Chen H. Established maternal obesity in the rat reprograms hypothalamic appetite regulators and leptin signaling at birth. Int J Obes (Lond) 2009;33:115-122.
15. Saben JL, Boudoures AL, Aghaz Z, et al. Maternal metabolic syndrome programs mitochondrial dysfunction via germline changes across three generations. Cell Rep 2016;16:1-8.
16. Qi L, Kang K, Zhang C, et al. Fat mass and obesity-associated (FTO) gene variant is associated with obesity: longitudinal analyses in two cohort studies and functional test. Diabetes 2008;57:3145-3151.
17. Kermack WO, McKendrick AG. Contributions to the mathematical theory of epidemics— I. 1927. Bull Math Biol 1991;51:33-55.
18. Ejima K, Aihara K, Nishiura H. Modeling the obesity epidemic: social contagion and its implications for control. Theor Biol Med Model 2013;10:17. doi:10.1186/1742-4682-10-17.
19. Turner J, Bansl L, Gilson R, et al. The prevalence of hepatitis C virus (HCV) infection in HIV-positive individuals in the UK – trends in HCV testing and the impact of HCV on HIV treatment outcomes. J Viral Hepat 2010;17:569-577.
20. Huang H, Yan Z, Chen Y, Liu F. A social contagious model of the obesity epidemic. Sci Rep 2016;6:37967. doi:10.1038/srep37967
21. Thomas DM, Weedermann M, Faemmeler BF, et al. Dynamic model predicting obesity, overweight, and extreme obesity prevalence trends. Obesity (Silver Spring) 2014;22:590-597.
22. Hong F, Kelley V, Molina-Serrano K, et al. A mathematical model to study the joint effects of genetics and diet on obesity. Arizona State University Mathematical and Theoretical Biology Institute. Article number MTBI-12-01. Published July 24, 2015. https://mtbi.asu.edu/sites/default/files/joint_effects_of_genetics_and_diet_on_obesity.pdf
23. Dawson JA, Dharurandhar EJ, Vazquez AI, Peng B, Allison DB. Propagation of obesity across generations: the roles of differential realized fertility and assortative mating by body mass index. Hum Hered 2013;75:204-212.
24. Anderson RM, May RM. Infectious Diseases of Humans: Dynamics and Control. New York, NY: Oxford University Press; 1991.
25. Zimmerman E, Angquist LH, Mirza SS, et al. Is the adiposity-associated FTO gene variant related to all-cause mortality independent of adiposity? Meta-analysis of data from 169,551 Caucasian adults. Obes Rev 2015;16:327-340.
26. Central Intelligence Agency. The World Factbook website. https://www.cia.gov/library/publications/the-world-factbook/ Accessed March 1, 2016.
27. Flegel KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. JAMA 2010;303:235-241.
28. Flegel KM, Krauss-Moran D, Carroll MD, Fryar CD, Ogden CL. Trends in obesity among adults in the United States, 2005 to 2014. JAMA 2015;315:2284-2291.
29. Stoor J, Bulirsch R. Introduction to Numerical Analysis. Vol 12, New York, NY: Springer Science & Business Media; 2013.
30. NHS Digital. Health survey for England, 2015: Trend tables. http://digital.nhs.uk/catalogue/PUB22616. Published December 14, 2016. Accessed July 3, 2017.
31. Timpson NJ, Emmett PM, Frayling TM, et al. The fat mass- and obesity-associated (FTO) gene works on obesity. Sci Rep 2015;5:15976. doi:10.1038/srep15976
32. Sorensen T, Ajslev TA, Angquist L, Morgen CS, Ciuchi IG, Davey Smith G. Obesity (Silver Spring). Vol 12. New York, NY: Springer; 2013.
33. NIH Digital. Health survey for England, 2015: Trend tables. http://digital.nhs.uk/catalogue/PUB22616. Published December 14, 2016. Accessed July 3, 2017.
34. Timpson NJ, Emmett PM, Frayling TM, et al. The fat mass- and obesity-associated locus and dietary intake in children. Am J Clin Nutr 2008;88:971-978.
35. Schmidt M, Hauser ER, Martin ER, Schmidt S. Extension of the SIMLA package for generating pedigrees with complex inheritance patterns: environmental covariates, gene-gene and gene-environment interaction. Stat Appl Genet Mol Biol 2005;4:Article15. doi:10.2202/1544-6115.1133
36. Linabery AM, Nahhas RW, Johnson W, et al. Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels Longitudinal Study. Pediatr Obes 2013;8:159-169.
37. Oliveria SA, Ellison RC, Moore LL, Gillman MW, Garrahie EJ, Singer MR. Parent-child relationships in nutrient intake: the Framingham Children’s Study. Am J Clin Nutr 2008;88:971-978.
38. Ajisefi TA, Angquist L, Silventoinen K, Baker JL, Sorensen TIA. Stable intergenerational associations of childhood overweight during the development of the obesity epidemic. Obesity (Silver Spring) 2015;23:1279-1287.
39. Fleten C, Nystad W, Stigum H, et al. Parent-offspring body mass index associations in the Norwegian Mother and Child Cohort Study: a family-based approach to studying the role of the intrauterine environment in childhood adiposity. Am J Epidemiol 2012;176:83-92.
40. Sorensen T, Ajisefi TA, Angquist L, Morgen CS, Czachi IG, Davey Smith G. Comparison of associations of maternal peri-pregnancy and paternal anthropometrics with child anthropometrics from birth through age 7 years evaluated in the Danish National Birth Cohort. Am J Clin Nutr 2016;104:389-396.