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

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Obesity epidemic model

As in **Figure 1** in the main text, the proportions of the population with and without obesity differed by genotype and are described by ordinary differential equations as follows:

$$\frac{dS_{aa}(t)}{dt} = \underbrace{\nu(1-k_1)c_a\left(S_{aa}+\frac{S_{Aa}}{2}\right)}_{\text{children born without obesity from the combination of paternal allele } a \text{ and maternal (without obesity) allele } a} +$$

$$\underbrace{\nu(1-k_2)c_a\left(I_{aa}+\frac{I_{Aa}}{2}\right)}_{\text{chlidren born without obesity from the combination of paternal allele } a \text{ and maternal (with obesity) allele } a} -$$

$$\underbrace{(\beta_{aa}I+\eta_{aa})S_{aa}}_{\substack{\text{progression to obesity}\\(S_{aa}\rightarrow I_{aa})}} - \underbrace{\mu S_{aa}}_{\text{natural death}} \quad \text{(A1)}$$

$$\frac{dI_{aa}(t)}{dt} = \underbrace{\nu k_1 c_a\left(S_{aa}+\frac{S_{Aa}}{2}\right)}_{\text{children born with obesity from the combination of paternal allele } a \text{ and maternal (without obesity) allele } a} +$$

$$\underbrace{\nu k_2 c_a\left(I_{aa}+\frac{I_{Aa}}{2}\right)}_{\text{children born with obesity from the combination of paternal allele } a \text{ and maternal (with obesity) allele } a} + \underbrace{(\beta_{aa}I+\eta_{aa})S_{aa}}_{\substack{\text{progression to obesity}\\(S_{aa}\rightarrow I_{aa})}} -$$

$$\underbrace{d_{aa}I_{aa}}_{\text{natural death and death due to obesity}} \quad \text{(A2)}$$

$$\frac{dS_{Aa}(t)}{dt} = \underbrace{\nu(1-k_1)c_A\left(S_{aa}+\frac{S_{Aa}}{2}\right)}_{\text{children born without obesity from the combination of paternal allele } A \text{ and maternal (without obesity) allele } a} +$$

$$\underbrace{\nu(1-k_2)c_A\left(I_{aa}+\frac{I_{Aa}}{2}\right)}_{\text{children born without obesity from the combination of paternal allele } A \text{ and maternal (with obesity) allele } a} +$$

$$\underbrace{\nu(1-k_1)c_a\left(S_{AA}+\frac{S_{Aa}}{2}\right)}_{\text{children born without obesity from the combination of paternal allele } a \text{ and maternal (without obesity) allele } A} +$$

$$\underbrace{\nu(1-k_2)c_a\left(I_{AA}+\frac{I_{Aa}}{2}\right)}_{\text{children born without obesity from the combination of paternal allele } a \text{ and maternal (with obesity) allele } A} -$$

$$\underbrace{(\beta_{Aa}I+\eta_{Aa})S_{Aa}}_{\substack{\text{progression to obesity}\\(S_{Aa}\rightarrow I_{Aa})}} - \underbrace{\mu S_{Aa}}_{\text{natural death}} \qquad \text{(A3)}$$

$$\frac{dI_{Aa}(t)}{dt} = \underbrace{\nu k_1 c_A\left(S_{aa}+\frac{S_{Aa}}{2}\right)}_{\text{children born with obesity from the combination of paternal allele } A \text{ and maternal (without obesity) allele } a} +$$

$$\underbrace{\nu k_2 c_A\left(I_{aa}+\frac{I_{Aa}}{2}\right)}_{\text{children born with obesity from the combination of paternal allele } A \text{ and maternal (with obesity) allele } a} +$$

$$\underbrace{\nu k_1 c_a\left(S_{AA}+\frac{S_{Aa}}{2}\right)}_{\text{children born with obesity from the combination of paternal allele } a \text{ and maternal (without obesity) allele } A} +$$

$$\underbrace{\nu k_2 c_a \left(I_{AA} + \frac{I_{Aa}}{2}\right)}_{\substack{\text{children born with obesity from the combination of} \\ \text{paternal allele } a \text{ and maternal (with obesity) allele } A}} + \underbrace{(\beta_{Aa} I + \eta_{Aa}) S_{Aa}}_{\substack{\text{progression to obesity} \\ (S_{Aa} \to I_{Aa})}} -$$

$$\underbrace{d_{Aa} I_{Aa}}_{\substack{\text{natural death and} \\ \text{death due to obesity}}} \qquad \text{(A4)}$$

$$\frac{dS_{AA}(t)}{dt} = \underbrace{\nu(1-k_1) c_A \left(S_{AA} + \frac{S_{Aa}}{2}\right)}_{\substack{\text{children born without obesity from the combination of} \\ \text{paternal allele } A \text{ and maternal (without obesity) allele } A}} +$$

$$\underbrace{\nu(1-k_2) c_A \left(I_{AA} + \frac{I_{Aa}}{2}\right)}_{\substack{\text{children born without obesity from the combination of} \\ \text{paternal allele } A \text{ and maternal (with obesity) allele } A}} -$$

$$\underbrace{(\beta_{AA} I + \eta_{AA}) S_{AA}}_{\substack{\text{progression to obesity} \\ (S_{AA} \to I_{AA})}} - \underbrace{\mu S_{AA}}_{\text{natural death}} \qquad \text{(A5)}$$

$$\frac{dI_{AA}(t)}{dt} = \underbrace{\nu k_1 c_A \left(S_{AA} + \frac{S_{Aa}}{2}\right)}_{\substack{\text{children born with obesity from the combination of} \\ \text{paternal allele } A \text{ and maternal (without obesity) allele } A}} +$$

$$\underbrace{\nu k_2 c_A \left(I_{AA} + \frac{I_{Aa}}{2}\right)}_{\substack{\text{children born with obesity from the combination of} \\ \text{paternal allele } A \text{ and maternal (with obesity) allele } A}} + \underbrace{(\beta_{AA} I + \eta_{AA}) S_{AA}}_{\substack{\text{progression to obesity} \\ (S_{AA} \to I_{AA})}} -$$

$$\underbrace{d_{AA} I_{AA}}_{\substack{\text{natural death and} \\ \text{death due to obesity}}} \qquad \text{(A6)}$$

where $S_{ij}(t)$ and $I_{ij}(t)$ denote the proportions of the population without and with obesity differed by genotype ij at year t, respectively. The frequency of each allele, c_a and c_A, is

described by N_{ij} as follows: $c_a = N_{aa} + \frac{N_{Aa}}{2}$, $c_A = N_{AA} + \frac{N_{Aa}}{2}$. **Figure 1** shows the schematic illustration of the transition between the populations.

Time-dependent dynamics of the genotype distribution

Assuming the mortality rate for people with obesity is same as that for people without obesity, and it is the same as the birth rate ($\nu = \mu$), the time-dependent dynamics of the genotype distribution, N_{aa}, N_{Aa}, N_{AA}, can be written by three ordinary differential equations:

$$\frac{dN_{aa}(t)}{dt} = \mu\left(N_{aa} + \frac{N_{Aa}}{2}\right)^2 - \mu N_{aa} \qquad \text{(A7)}$$

$$\frac{dN_{Aa}(t)}{dt} = 2\mu\left(N_{AA} + \frac{N_{Aa}}{2}\right)\left(N_{aa} + \frac{N_{Aa}}{2}\right) - \mu N_{Aa} \qquad \text{(A8)}$$

$$\frac{dN_{AA}(t)}{dt} = \mu\left(N_{AA} + \frac{N_{Aa}}{2}\right)^2 - \mu N_{AA} \qquad \text{(A9)}$$

where $N_{aa} + N_{Aa} + N_{AA} = 1$. The fixed point of this system can be solved by setting all the equation equal to zero: $(N_{aa}^*, N_{Aa}^*, N_{AA}^*) = \left(x, 1 + x - 2\sqrt{x}, 2\sqrt{x} - 2x\right)$.

x can take 0 to 1, which means the fixed point depends on the initial genotype distribution. Similarly, time-dependent dynamics of the proportion of the hypothetical obesogenic gene, $c_A = N_{AA} + \frac{N_{Aa}}{2}$, is derived by using equations (A7)-(A9);

$$\frac{dc_A(t)}{dt} = 0 \qquad \text{(A10)}$$

which means the proportion of the hypothetical obesogenic gene among the population is time constant.

Drop socially contagious risk and genetic effect

Hereafter, we drop the socially contagious risk ($\beta = 0$) and genetic effect (assume $\eta_{aa} = \eta_{Aa} = \eta_{AA}$) from the model. Then the difference from genotype disappears and the model can be reduced and solved as follows:

$$\begin{pmatrix} S' \\ I' \end{pmatrix} = M \begin{pmatrix} S \\ I \end{pmatrix} \quad \text{(A11)}$$

$$M = \begin{pmatrix} -\mu - \eta + \nu(1 - k_1) & \nu(1 - k_2) \\ \eta + \nu k_1 & -\mu + \nu k_2 \end{pmatrix} \quad \text{(A12)}$$

$$\begin{pmatrix} S \\ I \end{pmatrix} = f_1 e^{(\nu(k_2 - k_1) - \mu - \eta)t} \begin{pmatrix} 1 \\ -1 \end{pmatrix} + f_2 e^{(\nu - \mu)t} \begin{pmatrix} 1 \\ \frac{\nu k_1 + \eta}{\nu(1 - k_2)} \end{pmatrix} \quad \text{(A13)}$$

As $-\mu + \nu$ is the largest eigenvalue, the 2nd term in equation (A13) is dominant, so the converged prevalence can be written as follows:

$$\frac{\nu k_1 + \eta}{\nu(1 - k_2) + \nu k_1 + \eta} \quad \text{(A14)}$$

Now, using this equation, we assess the sensitivity of the obesity prevalence on the parameters. The best fit parameter set in **Table 2** is used as the baseline value. First, we see the sensitivity of the prevalence on phenotypic (nongenetic) transmission by changing k_2 (**Figure S1**). As k_2 increases, the obesity prevalence goes up, but the impact is quite limited. **Figure S2** shows the sensitivity on spontaneous weight gain rate η. As η goes up, the prevalence increases. **Figure S3** shows the sensitivity on ν. As ν goes up, the prevalence decreases.

Computational code for the obesity epidemic model (R code)

```
##library to solve differencial equation##
library(deSolve)
##define the obesity epidemic model##
si <- function(time, y, parameters) {
        with(as.list(c(y, parameters)), {
                mu=0.0144; d_aa=mu; d_Aa=mu; d_AA=mu; nu=mu
                Naa=Saa+Iaa
                NAa=SAa+IAa
                NAA=SAA+IAA
                I=Iaa+IAa+IAA
                ca = (2*Naa+NAa) / 2
                cA = (2*NAA+NAa) / 2
                dSaa <- nu*ca*((1-k1)*(Saa+SAa/2) + (1-k2)*(Iaa+IAa/2)) -
(beta_aa*I+eta_aa+mu)*Saa
                dIaa <- nu*ca*(k1*(Saa+SAa/2) + k2*(Iaa+IAa/2)) + (beta_aa*I+eta_aa)*Saa
- d_aa*Iaa
                dSAa <- nu*ca*((1-k1)*(SAA+SAa/2) + (1-k2)*(IAA+IAa/2)) + nu*cA*((1-
k1)*(Saa+SAa/2) + (1-k2)*(Iaa+IAa/2)) - (beta_Aa*I+eta_Aa+mu)*SAa
                dIAa <- nu*ca*(k1*(SAA+SAa/2) + k2*(IAA+IAa/2)) +
nu*cA*(k1*(Saa+SAa/2) + k2*(Iaa+IAa/2)) + (beta_Aa*I+eta_Aa)*SAa - d_Aa*IAa
                dSAA <- nu*cA*((1-k1)*(SAA+SAa/2) + (1-k2)*(IAA+IAa/2)) -
(beta_AA*I+eta_AA+mu)*SAA
                dIAA <- nu*cA*(k1*(SAA+SAa/2) + k2*(IAA+IAa/2)) +
(beta_AA*I+eta_AA)*SAA - d_AA*IAA
                list(c(dSaa, dIaa, dSAa, dIAa, dSAA, dIAA))
        })
}
##solve ODE model##
start=1988
times <- seq(start, start+200)
parameters <- c(k1=0, k2=0.070521963, beta_aa=0.004556391, beta_Aa=0.004556391,
beta_AA=0.284332946, eta_aa=0.000792872, eta_Aa=0.000792872, eta_AA=0.023607965)
init <- c(Saa=0.78*0.34, Iaa=0.22*0.34,
                  SAa=0.78*0.46, IAa=0.22*0.46,
                  SAA=0.78*0.20, IAA=0.22*0.20)
out <- as.data.frame(ode(y = init, times = times, func = si, parms = parameters))
out$time=seq(start, start+200)
##draw figure##
plot(out$time,(out$Iaa+out$IAa+out$IAA)*100,axes=FALSE,xlab="year",ylab="proportion
of population with obesity (%)",xlim=c(start, start+200),ylim=c(0,50),lty=1,bty = "l",
col=1,type="l")
par(new=T)
plot(c(start,start+11,start+19),c(22,30,32),axes=FALSE,xlab="",ylab="",xlim=c(start,
start+200),ylim=c(0,50),lty="blank",pch=16,col=1)
axis(side=1,at=c(seq(1990,2190,by=10)), tcl = -0.3, pos=0)
axis(side=2,at=seq(0,50,10), tcl = -0.5, las=1, pos=1988)
```

Tables

Table S1. Key assumptions relevant to the intergenerational transmission of obesity

Key assumptions	Supportive reference	Unsupportive reference
Obesity risk is dependent on prevalence of obesity (social contagion).	[1]	
Susceptibility to obesity differs by genotype.	[2,3]	
Maternal obesity has a causal effect on the risk that a child is born as obese (phenotypic transmission).	[4]	[5-7]
There is no assortative mating for BMI; i.e., the probability distribution of male BMI conditional on female mating-partner BMI is constant across the distribution of female mating-partner BMI (and vice versa).		[8]
Realized fertility is not associated with maternal obesity.		[9-11]
Genes and environment don't interact with each other on progression to obesity.		[12]
Paternal obesity does not have a causal effect on the probability of offspring obesity in childhood.		[13,14]
Role of mother on offspring obesity is the same as that of father except phenotypic transmission.		[15]
Mortality risk is independent from BMI.		[16]
Spontaneous waight gain risk is fixed over time		

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Figure Legends

Figure S1: Sensitivity of obesity prevalence on phenotypic (nongenetic) transmission of obesity.

The gray vertical line represents the baseline value of k_2.

Figure S2: Sensitivity of obesity prevalence on spontaneous weight gain rate.

The gray vertical line represents the baseline value of η.

Figure S3: Sensitivity of obesity prevalence on birth rate.

The gray vertical line represents the baseline value of ν.

Figure S4: Proportion of the population with obesity attributable to social contagious risk factors among the newly diagnosed cases (incidence) of obesity.

Obesity risk consists of spontaneous weight gain risk and social contagious risk after birth. The line shows the time course change in the proportion of new cases of obesity due to the social contagious risk factor.

Figures

Figure S1

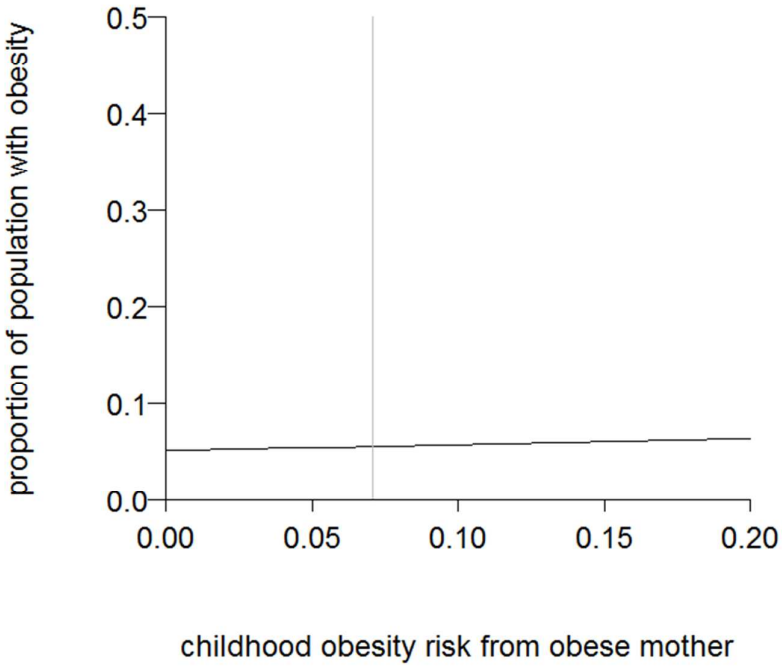


Figure S2

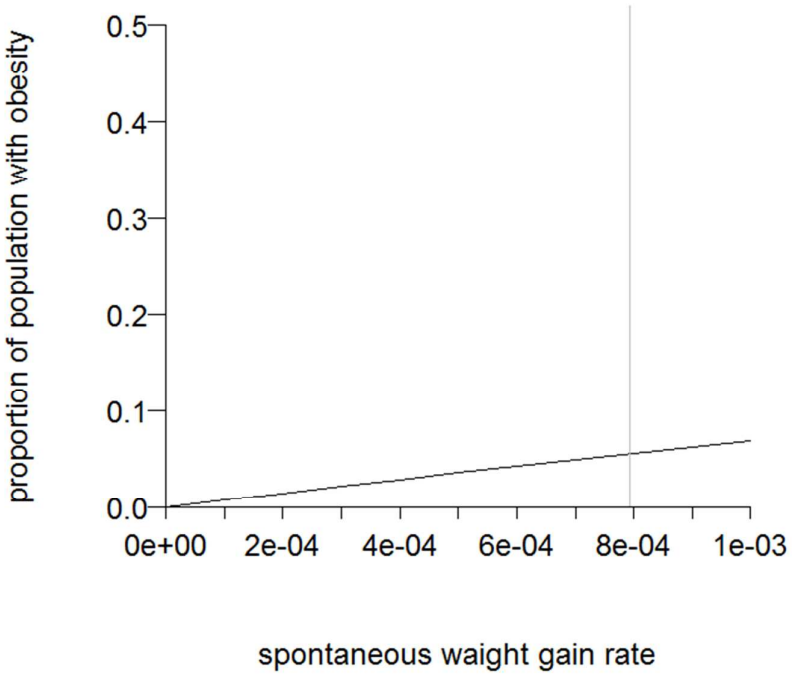

proportion of population with obesity
0.5
0.4
0.3
0.2
0.1
0.0
0e+00
2e-04
4e-04
6e-04
8e-04
1e-03
spontaneous waight gain rate

Figure S3

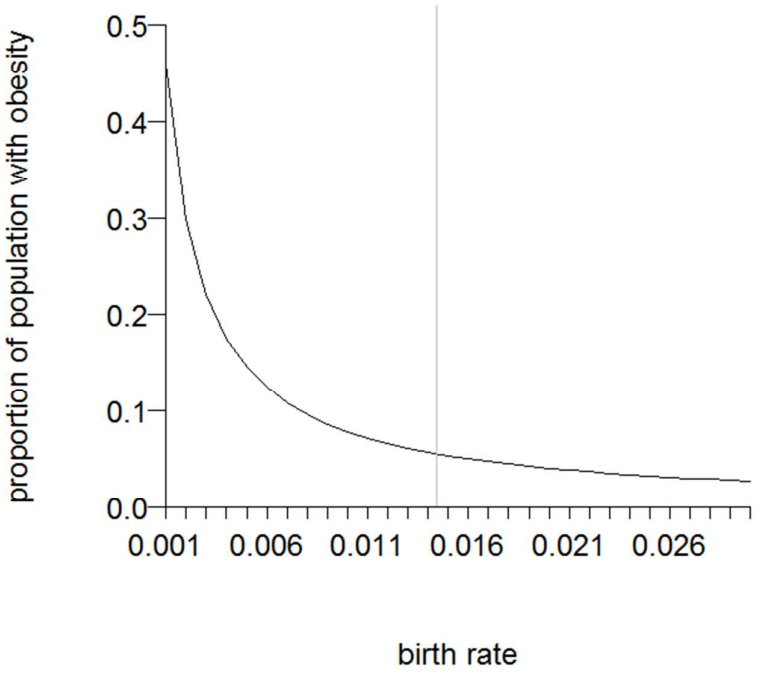
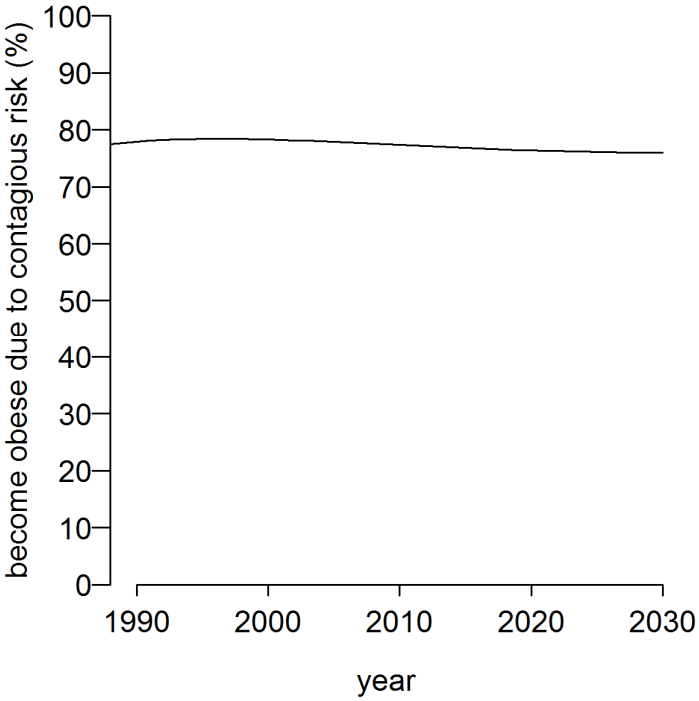

proportion of population with obesity
0.5
0.4
0.3
0.2
0.1
0.0
0.001
0.006
0.011
0.016
0.021
0.026
birth rate

Figure S4


become obese due to contagious risk (%)
100
90
80
70
60
50
40
30
20
10
0
1990
2000
2010
2020
2030
year