



# Adoption study of environmental modifications of the genetic influences on obesity

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**BACKGROUND:** Adult body mass index (BMI weight (kg)/height<sup>2</sup> (m<sup>2</sup>)) usually shows familial correlations below 0.3, which are almost entirely due to genetic influences. The considerable remaining non-familial individual variation may be due to non-shared environmental influences which, however, may interact with or modify the genetic influence.

**OBJECTIVE:** To investigate whether the genetic influence on adult BMI is modified by various obesity-related environmental conditions during childhood and adulthood.

**DESIGN:** Adoption study, in which the genetic influence is assessed by the correlations in adult BMI between adoptees and their biological fathers, mothers and full siblings. These correlations were compared between groups of families characterized by differences in rearing or adult environment of the adoptees and/or their biological relatives.

**SUBJECTS:** Height, current weight and greatest weight ever, were obtained in 3651 subjects, who were adopted by non-related families in Copenhagen between 1924 and 1947. Groups representing thin, medium weight, overweight and obese proband adoptees were selected by current BMI ( $n = 540$ ) and by maximum BMI ( $n = 524$ ). The members of the biological and adoptive families of the proband adoptees were identified and their BMI was computed from height and weight obtained by mailed questionnaires.

**MAIN VARIABLES:** Indicators related to the rearing environment of the adoptees were age of the adoptee at transfer to the adoptive family, region of residence, presence of adoptive siblings and, for the adoptive parents, year of birth, age at time of adoption, occupational rating, smoking habits and BMI. Indicators of the environment of both the adoptee and the biological relatives were: year of birth; occupational rating and smoking habits, and, of the environment of the biological parents, age and parity at birth of the adoptee.

**RESULTS:** The correlations in BMI between adoptees and the biological fathers, mothers and siblings were 0.11, 0.15 and 0.26 for adoptees selected by current BMI, and 0.13, 0.16, and 0.27 for adoptees selected by maximum BMI, respectively (all  $P < 0.001$ ), demonstrating the previously reported genetic influence. None of the environmental indicators showed consistent and significant effects on these six correlations. The same negative results were obtained in analysis of environmental indicators applied to the two adoptive parents together or to the adoptee and the biological relatives together.

**CONCLUSION:** The genetic influence on BMI was unaffected by several different environmental conditions otherwise associated with obesity.

**Keywords:** adoption study; body mass index; environmental indicators; familial occurrence; genetics; obesity; smoking; social class

## Introduction

Measures of fatness, including the body-mass index (BMI weight (kg)/height<sup>2</sup> (m<sup>2</sup>)), are correlated among adult relatives, at about 0.2 between parent-offspring and about 0.3 between siblings.<sup>1</sup> Studies of twins and adoptees have shown that the familial resemblance among adults is due to the genes they have in common rather than to their shared environment.<sup>2,3</sup> The size of the familial correlations shows, however, that a considerable proportion of the interindividual differences

in BMI is probably due to differences in non-shared environmental influences.<sup>4</sup>

It is possible that genetic and environmental factors exert their effects independent of each other. An alternative hypothesis is that the genetic and environmental factors interact and modify the influences of each other on the body mass index. We pose here the question whether there are environmental conditions that modify the genetic influences. To investigate this, we estimated the genetic influences by the correlations in body mass index between adult adoptees and their biological first-degree relatives, that are the father, mother and full siblings.<sup>4-7</sup> These correlations were then compared between groups of families in which the adoptees and/or the biological relatives, according to various environmental indicators, had been exposed to different environments during childhood or adulthood.

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We have assessed the influence of the following environmental indicators related to the rearing environment of the adoptee: region of residence of the adoptive family at time of adoption, age of the adoptee at transfer to the adoptive family, presence of adoptive siblings in the family, and, for the adoptive parents, year of birth, age at time of adoption, social class, as rated by occupation, and smoking habits. Indicators of the environment of both the adoptees and their biological relatives were year of birth, occupational rating and smoking habits, and, of the environment of the biological parents, age and parity at birth of the adoptee.

We have previously reported that there was no correlation in body mass index between the adoptees and the adoptive parents,<sup>3-5,7</sup> which indicated that the familial rearing environment does not contribute to the familial correlation of adult body mass index. However, since this does not preclude that the body mass index of these parents could be an indicator of some environmental factors that may modify the genetic influence in the adoptee, we have analyzed this possibility as well.

## Subjects and methods

The 5455 non-familial adoptions granted in the Copenhagen area between 1924 and 1947 form the basis for the study population.<sup>5-8</sup> Adoptees were usually separated from their biological mothers immediately after birth and either transferred directly to the adoptive parents or reared in foster homes until adoption.

Of 4643 adoptees still living in Denmark, 3651 (79%) replied to a postal questionnaire asking for height, current weight and greatest weight they had ever had. The responses were complete for height and current weight in 3580 and for height and maximum weight in 3476 adoptees. Mean (s.d.) age of the adoptees was 42.2 y (8.1) y, and 56% were women.

Current and maximum body mass index (maximum weight/current height<sup>2</sup>) was calculated. Four groups of proband adoptees were selected, on the basis of current body mass index (thin, medium weight, overweight and obese) each comprising 4% of the population, total  $4 \times 137 = 548$  adoptees. A similar selection was carried out on the basis of maximum body mass index, comprising  $4 \times 133 = 532$  adoptees. Of the total of 840 selected proband adoptees, 240 belonged to both groups. Due to reporting errors, discovered after a second survey, the size of the two selected groups was reduced to 540 and 524 adoptees, respectively.<sup>5,7</sup> The selection took place within  $2 \times 5$  gender-age strata. As described below, the technique for analysis of the data has been tailored to this sampling scheme.

The adoption records and other population registers allowed identification and follow up of the biological and adoptive parents and siblings of the proband adoptees. Information on height and weight of these

family members was sought by mailed questionnaires. In order to make the age at assessment of the parents comparable to that of the adoptees, parents reported their height and weight at an age when their offspring went to school. The proband adoptees and the siblings were asked about their height, current weight and greatest weight ever, and about the height and weight of their father and mother.

Further details of the study as well as the principles and assumptions of the adoption method have been previously reported.<sup>4-8</sup>

### Environmental indicators

The adoption register records, filled out at the time of adoption, provided information about dates of birth of the adoptee and the biological and adoptive parents, age of the adoptee at transfer to the adoptive parents, region of residence of the adoptive parents and occupation of the biological parents and the adoptive father.

The identification and follow-up of the family, in the population registers, provided information about the dates of birth for any other children of the adoptees biological mother and about other children present in the adoptive family.

The mailed questionnaires yielded information about height and weight of the adoptive parents at the time the adoptee went to school, occupation of the adoptee and biological siblings, and smoking habits of the adoptee, the biological parents and siblings and the adoptive parents.

Environmental indicators were used in dichotomized form with quantitative traits divided at values close to their median. Region of residence was divided into within, and outside, the greater Copenhagen area, corresponding to living in metropolitan vs rural areas. Information about children other than the adoptee in the adoptive home was coded as presence or absence of adoptive siblings. The position of the adoptee in the birth order of offsprings of the biological mother was coded as first vs later born, and as born as the 1st through 3rd child vs born as the 4th or later. The occupation was rated on a prestige-based scale ranging from 0 (for unskilled manual workers) to 7 (for the highest senior academic and business positions).<sup>9</sup> In order to get a fairly balanced number of subjects in either group, we divided the occupational rates according to the distribution of the subjects across the scale; for the adoptive fathers and the adoptees and their siblings the division was at 0-2 vs 3-7; for the biological fathers it was 0-1 vs 2-7 and for the biological mothers, 0 vs 1-7. Smoking was recorded as daily smoking vs not daily smoking.

### Strategy of analysis

The relationship between body mass index of family members were expressed as correlation coefficients. This was judged an appropriate statistical measure to use, in view of the fairly linear relationship previously observed in this and other studies across the entire

**Table 1** Correlations in current and maximum body mass index (BMI) between adult adoptees and their biological fathers, mothers and full siblings<sup>a</sup>

Biological relative of adoptee	Current BMI			Maximum BMI		
	<i>n</i>	<i>r</i>	<i>P</i>	<i>n</i>	<i>r</i>	<i>P</i>
Father	269	0.11	0.001	266	0.13	0.0003
Mother	344	0.15	0.00001	335	0.16	0.00000
Siblings	115 (57) <sup>b</sup>	0.26	0.00005	127 (64) <sup>b</sup>	0.27	0.00002

<sup>a</sup>The correlations and the *P* values deviate slightly from those previously published,<sup>7</sup> because the present analysis is based on a common estimate across a stratification by year of birth of the adoptees (before 1940 vs 1940 or later).

<sup>b</sup>Number of families.

range of body mass index.<sup>1,5,6</sup> Six family relationships were examined: for adoptees selected on the basis of current and maximum body mass index, respectively, we examined the three relationships, adoptee vs biological mother, adoptee vs biological father and adoptee vs biological full siblings (Table 1). Current and maximum body mass index of the adoptees and their siblings was used for the respective series of correlation analysis; for the analysis including the parents, we used their body mass index at around the age when their offspring went to school.

For each of these six family relationships, we estimated two correlations, one for each of the two classes of the environmental indicators. We then tested whether the correlations were equal in the two classes of the environmental indicator (Figure 1).

The same environmental indicators were available for both the adoptees and the biological relatives for year of birth, occupational rating and daily smoking. This information improved the likelihood of detecting effects of these indicators.<sup>10,11</sup> For example, the indicator variable about daily smoking for the adoptee and for the biological relative was combined as follows: 1) both non-smokers; 2) mixed group, with either the adoptee or the biological relative being smokers and 3) both smokers. Similar combinations were constructed for year of birth and occupational rating.

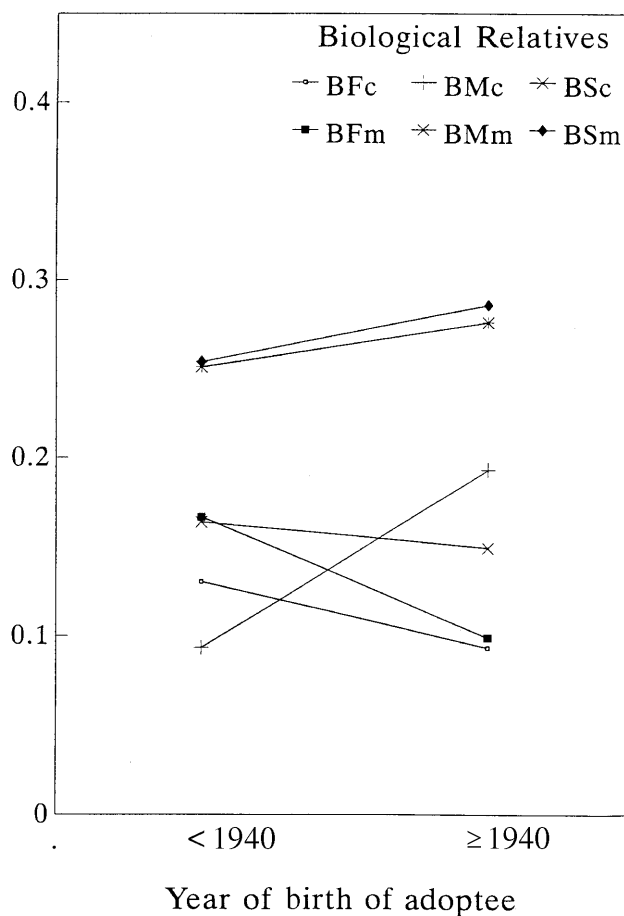
The possibility of detecting the effects of the environmental indicators related to the adoptive parents was also increased by combining the two parents in the same analysis. For example, the body mass index of the adoptive fathers and mothers was combined to: 1) 'thin', where both parents had a low body mass index; 2) a mixed group, comprising the parents that had either low or high body mass index, respectively and 3) 'heavy', where both parents had high body mass index.

The six family correlations were then estimated within each of the three classes of the combined indicator variables and tested for significant differences between these classes.

### Statistical analysis

Asymptotically unbiased estimates of the correlations were obtained, and their deviations from zero were

### Correlation



**Figure 1** Correlations in current (c) and maximum (m) body mass index between adult adoptees and their biological relatives (fathers, BF; mothers BM; full sibling, BS). The correlations were estimated separately in families where the adoptees were born before 1940 and in 1940 or later. None of the differences between the correlations in these two groups were statistically significant.

tested. The truncated distribution of the body mass index, due to the selective sampling of adoptees within gender-age strata, was taken into account. In estimating the sibling correlations, all available siblings of the adoptee were included in the analysis. Details of the estimation procedure have been described elsewhere.<sup>7</sup>

The procedures for, and the assumptions of, the estimation of the correlations in the classes of the environmental indicators and for testing of the null hypothesis that the correlations are equal across these classes, are described in the Statistical Appendix.

A total of 166 tests of correlation differences (6 family relationship with each of 28 environmental indicator variables, except for one variable with only 4 relationships) were performed. Nineteen, 10, 7, and 1 tests resulted in *P* values less than 0.1, 0.05, 0.025, and 0.01, respectively. To avoid the risk of type 1 errors, we also considered, in addition to the statistical evaluation of the six pairs of correlations for each environmental indicator, the consistency of the results across the six relationships. The within-pair differ-

ences of the six pairs of correlations were calculated and the results were presented as the median and range of these correlation differences. For the combined analyses of environmental indicators, the results are based on the differences between the extreme levels (classes 1 and 3). According to the non-parametric Wilcoxon test for matched pairs, uniform direction of differences of six pairs are significant at the 0.05 level.<sup>12</sup>

## Results

Table 1 shows the three correlations between current body mass index of the adoptees and the biological relatives (the fathers, mothers and full siblings) and the three corresponding correlations of maximum body mass index. All the correlations were highly statistically significant. Also shown in Table 1 are the number of subjects entered in this analysis. In the subsequent analyses, the numbers available may be smaller because of missing information about the environmental indicators for some individuals.

Figure 1 shows the correlations in current and maximum body mass index between the adoptees and their biological relatives for families in which the adoptees were born before 1940, during 1940 or later. All 12 correlations were significantly different

from zero (all  $P < 0.05$ ). Three out of six correlations for adoptees born before 1940 were lower, and three were higher, than the corresponding correlations for adoptees born during 1940 or later. The pairwise differences between the correlations at the two levels of the indicator ranged from  $-0.09$  to  $0.07$  with a median difference at  $-0.005$  and none of these differences were significantly different from zero. Thus, the year of birth of the adoptee did not significantly modify the correlations in body mass index between adoptees and their biological relatives.

The indicators related to the rearing environment, were some characteristics of the adoptive family, (age of the adoptee at transfer to the adoptive family, region of residence and presence of adoptive siblings), and some characteristics of the adoptive fathers and mothers (year of birth, age at the time of adoption, occupational rating, daily smoking and body mass index) (Table 2). The median values and ranges of the differences between the correlations in the two classes of each of the environmental indicators make it clear that none of them had any influence. All correlation differences, except for one (the adoptive fathers daily smoking), showed ranges encompassing zero and very few differences were significant. Smoking by the adoptive mothers or by the adoptive parents combined, did not show the same uniform effects as smoking by the adoptive fathers.

The median correlation differences suggest that there was a trend towards higher correlations between

**Table 2** Effects of indicators related to the rearing environment of the adoptees: median values and ranges of the differences between correlations of body mass index (BMI) of adoptees and their biological relatives in different classes of the environmental indicators

Environmental indicators	Dichotomy classes	Correlation differences <sup>a</sup>		Number of significant differences <sup>b</sup>
		Median	Range	
<b>Adoptive family</b>				
Age (months) of adoptee at transfer	0–3 vs $\geq 4$	–0.01	–0.03–0.07	0
Residence in Copenhagen	No vs Yes	0.00	–0.05–0.24	0
Presence of adoptive siblings	No vs Yes	–0.04	–0.17–0.15	1
<b>Adoptive father</b>				
Year of birth	before 1904 vs 1904 or later	–0.07	–0.14–0.03	1
Age (y) at adoption	< 34 vs $\geq 34$	0.03	–0.07–0.13	0
Occupational rating <sup>c</sup>	0–2 vs 3–7	0.05	–0.09–0.08	0
Daily smoking <sup>d</sup>	No vs Yes	0.04	0.01–0.11	0
BMI (kg/m <sup>2</sup> )	< 25 vs $\geq 25$	–0.06	–0.12–0.13	0
<b>Adoptive mother</b>				
Year of birth	before 1906 vs 1906 or later	–0.04	–0.17–0.13	1
Age (y) at adoption	< 34 vs $\geq 34$	0.02	–0.10–0.10	0
Daily smoking	No vs Yes	0.02	–0.09–0.06	0
BMI (kg/m <sup>2</sup> )	< 23.5 vs $\geq 23.5$	–0.07	–0.12–0.13	0
<b>Adoptive parents combined<sup>e</sup></b>				
Year of birth	Early vs Late	–0.07	–0.18–0.10	1
Age at adoption	Young vs Old	0.04	–0.07–0.18	0
Daily smoking	None vs Both	0.09	–0.02–0.28	0
BMI (kg/m <sup>2</sup> )	Thin vs Heavy	–0.11	–0.33–0.42	0

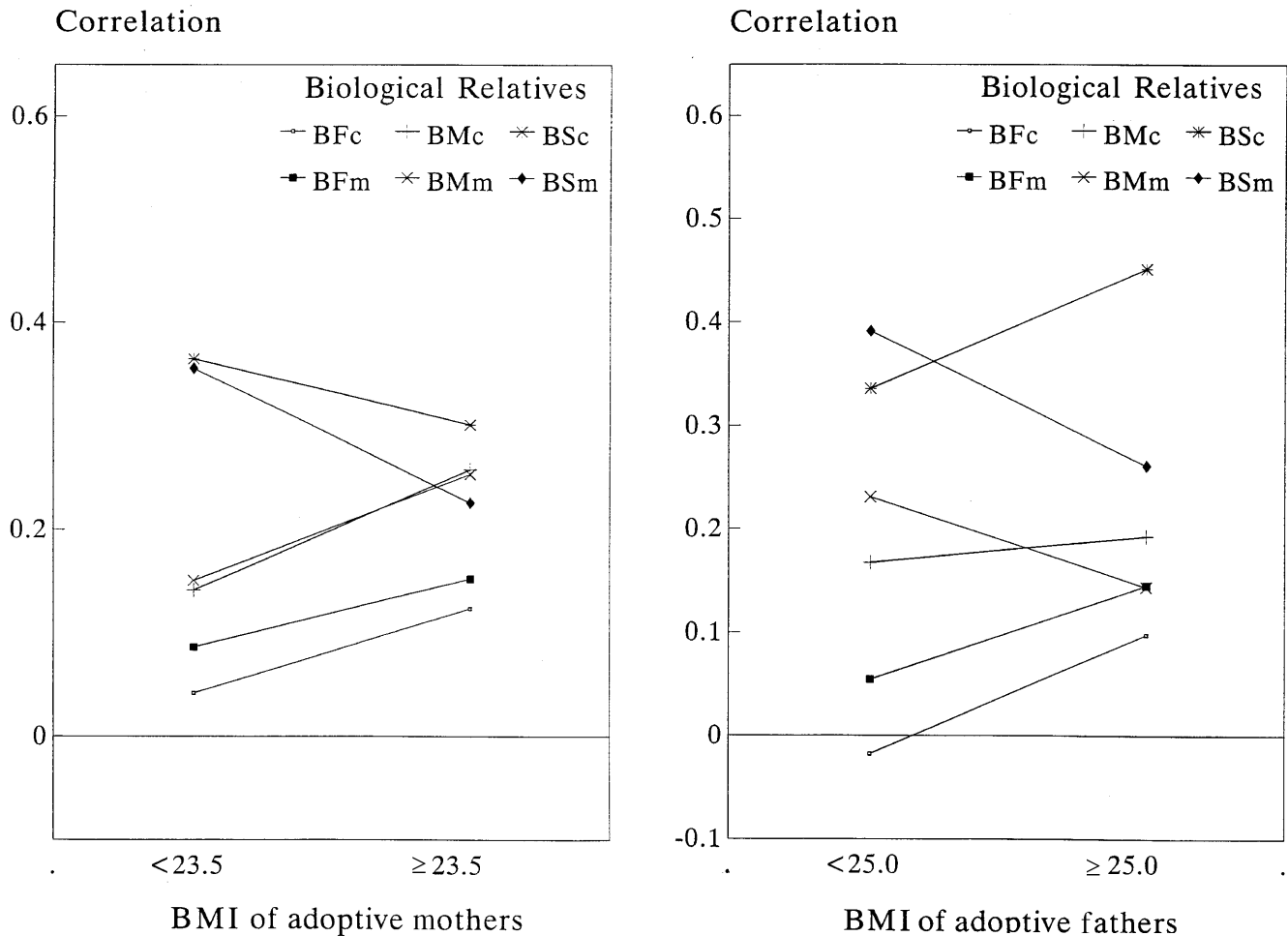
<sup>a</sup>Within pair differences of the six pairs (three for current and three for maximum BMI of the adoptees) of correlations between the adoptees and their biological relatives in the two classes of the environmental indicators: the correlations in the first class minus the correlations in the second class (compare with Figure 1).

<sup>b</sup>Each of the six pairs of correlations were tested for significant differences ( $P < 0.05$ ).

<sup>c</sup>Prestige-based rating with 0 as the lowest rate, see text for further explanation.

<sup>d</sup>All adoptive fathers, except two, were daily smokers in the families with biological siblings of the adoptees selected on the basis of current BMI, so the pertaining correlations could not be estimated.

<sup>e</sup>The correlations were estimated for the combinations of the lowest classes of the environmental indicator for the adoptee and respective relative, and compared to the corresponding correlations estimated for the highest classes.



**Figure 2** Correlations in body mass index (BMI) between adoptees and their biological relatives in two groups of families where the adoptive mothers had a BMI either lower or greater than 23.5 kg/m<sup>2</sup> (left), and in two groups of families where the adoptive fathers had a BMI either lower or greater than 25.0 kg/m<sup>2</sup> (right).

the adoptees and their biological relatives if the adoptive parents had a high body mass index than if they had a low body mass index (Table 2). However, none of the correlation differences were significant, and the differences were not in the same direction across all the relationships (Figure 2).

The indicators presumed to be related to the adult environment of the adoptees and the biological relatives, did not consistently influence the correlations between these subjects and very few correlation differences were significant (Table 3).

The correlations between the adoptees and their biological relatives proved to be consistently higher for the adoptees who were born first than for the adoptees who were born later (median correlation difference was 0.07 and the range was from 0.03 to 0.37; the greatest difference was significant ( $P < 0.02$ )). There were, however, no significant differences between correlations for adoptees being among the first three children born compared to adoptees born later (range  $-0.04 - 0.08$ ; median 0.04).

Daily smoking of the biological relatives also showed differences in correlations in the same direction for all six relationships, but none were significant. No similar effect was seen with regard to the adoptee

smoking or when smoking was considered for adoptees and the biological relatives in the same analysis. Moreover, the effect on the correlations, was in the opposite direction of that seen for smoking by the adoptive parents.

## Discussion

This study found no consistent and statistically significant effects of a variety of environmental indicators on the correlations in body mass index between adoptees and their biological first degree relatives. This suggests that the genetic effects on adult fatness are not influenced by the environmental conditions that we investigated, which by themselves may influence the degree of fatness.

Only few studies have specifically addressed the question of environmental modification of the genetic influence on fatness – or the question of genetic modifications of the environmental influences. One reason is that this type of study requires access to populations in which subjects with known differences in genetic background can be compared with respect

**Table 3** Effects of indicators assumed to be related to the adult environment of the adoptees and their biological relatives: median values and ranges of the differences between correlations of body mass index (BMI) of adoptees and their biological relatives in different classes of the environmental indicators

Environmental indicators	Dichotomy classes	Correlation differences <sup>a</sup>		Number of significant differences <sup>b</sup>
		Median	Range	
<b>Adoptee</b>				
Year of birth	before 1940 vs 1940 or later	-0.01	-0.09-0.07	0
Occupational rating <sup>c</sup>	0-2 vs 3-7	0.06	-0.07-0.14	0
Daily smoking	No vs Yes	-0.01	-0.16-0.11	1
<b>Biological relatives<sup>d</sup></b>				
Year of birth	Early vs Late	-0.01	-0.29-0.05	0
Age at birth of adoptee	Young vs Older	-0.01	-0.37-0.05	1
Parity at birth of adoptee	1 vs > 2	0.07	0.03-0.37	1
	1-3 vs > 4	0.03	-0.04-0.08	0
Occupational rating	Low vs High	-0.13	-0.29-0.08	1
Daily smoking	No vs Yes	-0.05	-0.17--0.01	0
<b>Adoptee and relatives combined<sup>e</sup></b>				
Year of birth <sup>f</sup>	Early vs Late	0.02	-0.12-0.06	1
Occupational rating	Low vs High	0.08	-0.03-0.20	0
Daily smoking	None vs Both	-0.02	-0.19-0.61	1

<sup>a</sup>Within pair differences of the six pairs (three for current and three for maximum BMI of the adoptees) of correlations between the adoptees and their biological relatives in the two classes of the environmental indicators: the correlations in the first class minus the correlations in the second class (compare with Figure 1).

<sup>b</sup>Each of the six pairs of correlations were tested for significant differences ( $P < 0.05$ ).

<sup>c</sup>Prestige-based rating with 0 as the lowest rate, see text for further explanation.

<sup>d</sup>Dichotomy levels are different for the three types of biological relatives: For year of birth: father before 1912 vs 1912 or later; mother, before 1916 vs 1916 or later; siblings, before 1940 vs 1940 or later. For age at birth of the adoptee: father, < 27 vs  $\geq 27$  y; mother, < 23 vs  $\geq 23$  y; siblings, born before or after the adoptee.

For occupational rating: father, 0-1 vs 2-7; mother, 0 vs 1-7; siblings, 0-2 vs 3-7.

<sup>e</sup>The correlations were estimated for the combinations of the lowest classes of the environmental indicator for the adoptee and respective relative, and compared to the corresponding correlations estimated for the highest classes.

<sup>f</sup>The siblings of the adoptees were not included in this analysis.

to the effects of different environmental influences.<sup>10,11,13</sup> It is important to distinguish the possible modifying effects studied here from those of correlations between genetic and environmental factors, which would imply that occurrence of genetic predisposition to fatness or obesity was related to exposure to the environmental factors influencing these traits.

It is widely believed that fatness and its extreme variant, obesity, results from some form of gene-environment interaction, implying that genes and environment do not act independent of each other.<sup>1</sup> Little is known, however, about how genes and environmental factors operate.

In principle, investigation of gene-environment interaction may be simple, if it deals with a monogenic disease or trait and a suspected specific environmental factor. Even more so, if the presence or absence of the disease-predisposing gene and the environmental factor can be ascertained.<sup>10,11</sup> However, the study of fatness and obesity is not in such favorable position. Monogenic human obesity is very rare,<sup>1</sup> and mutations in the newly discovered *ob*-gene, associated with obesity in rodents, are extremely rare in human obesity.<sup>14,15</sup> Human fatness and obesity, appears to be a polygenic condition, probably with a considerable genetic heterogeneity between individuals of similar degree of fatness.

There is, however, some indirect evidence supporting the idea that one or more major genes interacting with the environment may play a role in human

obesity.<sup>1</sup> Commingling analysis of the distribution of body mass index of monozygotic twins shows that it is compatible with an admixture of at least two component distribution, one for the upper extreme, and another for the remaining part, of the population.<sup>16</sup> The correlation between the twin pairs in the upper component is far lower than that among pairs in the lower component, suggesting a greater susceptibility to environmental influences in the upper component. Commingling analysis of the secular changes in the distribution of body mass index shows that the increasing prevalence of obesity may be described as an increasing size of an upper component distribution, which may reflect the result of general changes in environmental factors acting on a genetically susceptible fraction of the population.<sup>17</sup> Unfortunately, the data of the present study do not allow investigation of environmental modifications of commingling distributions.

In both mouse and man, there appears to be a genetic variation in weight gain, in response to diets with different fat content.<sup>18,19</sup> In a prospective population-based cohort study of women in Gothenburg,<sup>19</sup> those with familial predisposition to obesity showed large weight gain in response to a high-fat diet, but no weight gain in response to a low-fat diet. Those without familial predisposition did not differ in weight gain at different amounts of dietary fat. The specific genetic basis in mouse and man for the different sensitivity to dietary fat, has not yet been identified.

Experimentally altered environments of human subjects, with different genetic make-up, may contribute to elucidation of gene-environment interaction. Bouchard and co-workers<sup>20,21</sup> conducted two such studies, in which 12 and seven pairs of monozygotic twins were exposed either to prolonged increases in dietary energy intake or to increased energy expenditure by controlled physical activity, respectively. They showed far larger between-pair than within-pair variation in changes of both general and regional obesity. Although differences in preceding and current environmental influences both between and within twin pairs cannot be excluded, the most likely explanation of the differences between the twin pairs is that the genetic differences between them determine the response to the controlled changes in the environment.

Most of the environmental influences, assessed in the present study, have been related to fatness or obesity in previous studies. Effects of year of birth, which here corresponds to age at examination, implies either secular trends or age differences in environmental influences,<sup>22,23</sup> which, however, cannot be disentangled within a single cross-sectional survey. There is some, although conflicting, evidence suggesting that the perinatal environment may influence adult obesity.<sup>24–26</sup> The ages of the adoptees and the adoptive parents at adoption indicate the time from which the familial environmental influences may operate in the adoptive family (the age of the adoptee at transfer, cannot be used as an indicator of duration of exposure to the environment of the biological family, because the adoptee was usually separated from the biological parents at birth and stayed in an intermediary environment until transfer to the adoptive family). Living in rural regions, being a single child, having parents of low social class, being in a low social class oneself, being a non-smoker and having several children, are associated with increased prevalence of obesity.<sup>1,9,22,27–29</sup> The possible effects of unfulfilled parenthood on the biological parents, following adoption of their child, may be related to their age at the birth.

Previous analysis of the present adoption study showed that the body mass index of the adoptive parents was not correlated with the body mass index of the adult adoptees, but there was a weak correlation in body mass index of the adoptive mother and the adoptees while they were still living together.<sup>30</sup> We found, however, no evidence suggesting that parental body mass index is an indicator of environmental influences in the family that might modify genetic influences later in life.

Another, smaller adoption study also found no evidence of environmental effects interacting with the genetic effects.<sup>31</sup> This study of 357 adult adoptees from Iowa confirmed the genetic influence on body mass index and the absence of relation to the adoptive parents' body mass index. It also showed that body mass index was increased by two environmental factors—rural (*vs* urban) environment and a disturbed

rearing environment due to psychopathology, alcoholism or drug abuse among adoptive relatives or death or divorce of the adoptive parents.

The nature and limitations of the two studies imply that we cannot preclude presence of interaction between genetic and environmental effects. The two studies were not comprehensive surveys of putative environmental factors possibly modifying the genetic influence. Notably, they included no information on two key elements of the energy balance equation—food (especially fat) intake and physical activity.<sup>1,18–21</sup> Furthermore, the data were obtained in cross-sectional surveys, but several of the environmental influences were pertinent only at some preceding period of the subjects' lives. The familial correlations in body mass index were, as previously discussed,<sup>7</sup> somewhat attenuated due to the errors of reported height and weight compared to measured data. Finally, some statistical power was sacrificed by the need for dichotomous indicator variables because the sampling design and the information available did not permit more sensitive and appropriate quantitative analyses.<sup>32</sup>

In conclusion, the study showed that a variety of pertinent environmental factors had no or little modifying effects on the genetic influence on body fatness or obesity.

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## Statistical appendix

Selective sampling will bias the usual Pearson product-moment estimator of correlation.<sup>33,34</sup> We have used the following alternative method to produce asymptotically unbiased estimates of the correlations.

Let  $y_i$  denote the body mass index (BMI) of an adoptee and let  $x_i = (x_{ij})_{j=1, \dots, n_i}$  denote the BMI of a given type of relative(s), of whom there may be one ( $n_i = 1$ ) or more ( $n_i > 1$ ). Assume that  $y_i$  and  $x_i$  has a joint normal distribution with parameters:

$$\begin{aligned} E(y_i) &= \mu_{ys} & V(y_i) &= \sigma_{ys}^2 \\ E(x_{ij}) &= \mu_{xs} & V(x_{ij}) &= \sigma_{xs}^2 \\ \text{Corr}(x_{ij}, x_{ik}) &= \rho_{xxs} & \text{Corr}(x_{ij}, y_i) &= \rho_{xys} \end{aligned}$$

for any individual from the population belonging to stratum  $s$ . The observations  $x_i$  are obtained only for the selected adoptees. The likelihood  $L$  of the joint distribution of a selected family may be factorized as:

$$L(y_i, x_i) = L(x_i|y_i) \times L(y_i)$$

If the stratification variable  $s$  is observed in the entire adoptee population, then the parameters  $\mu_{ys}$  and  $\sigma_{ys}^2$  may be estimated from  $y_i$  in this population. So, with regard to the selected sample, they are assumed to be known. The unknown parameters enter only through  $L(x_i|y_i)$ . This conditional distribution is normal with:

$$\begin{aligned} E(x_{ij}|y_i) &= \alpha_{x:ys} + \beta_{x:ys}y_i \\ V(x_{ij}|y_i) &= \sigma_{x:ys}^2 \\ \text{Corr}(x_{ij}, x_{ik}|y_i) &= \rho_{xx:ys} \end{aligned}$$

where:

$$\begin{aligned} \alpha_{x:ys} &= \mu_{xs} - \rho_{xys} \frac{\sigma_{xs}}{\sigma_{ys}} \mu_{ys} \\ \beta_{x:ys} &= \rho_{xys} \frac{\sigma_{xs}}{\sigma_{ys}} \\ \sigma_{x:ys}^2 &= \sigma_{xs}^2 (1 - \rho_{xys}^2) \\ \rho_{xx:ys} &= (\rho_{xxs} - \rho_{xys}^2) / (1 - \rho_{xys}^2). \end{aligned}$$

These equations are easily solved with respect to the unconditional parameters:

$$\begin{aligned} \mu_{xs} &= \alpha_{x:ys} + \beta_{x:ys} \mu_{ys} \\ \sigma_{xs}^2 &= \sigma_{x:ys}^2 + \beta_{x:ys}^2 \sigma_{ys}^2 \\ \rho_{xys} &= \beta_{x:ys} / \sqrt{\frac{\sigma_{x:ys}^2}{\sigma_{ys}^2} + \beta_{x:ys}^2} \\ \rho_{xxs} &= \rho_{xx:ys} (1 - \rho_{xys}^2) + \rho_{xys}^2. \end{aligned}$$

The maximum likelihood estimates of the unconditional parameters are then obtained by maximizing  $l = \sum_i \ln L(x_i|y_i)$  with respect to the conditional parameters and solving the equations given above with respect to the unconditional parameters.

In this study the stratification variable  $s$  is a combination of a stratification by year of birth of the adoptees (before 1940 vs 1940 or later) and the environmental indicators from Table 2 and Table 3. First it is examined whether the correlations are equal across the two strata defined from year of birth. This is tested by maximizing  $l$  with the relevant correlations set equal and taking twice the difference between the two maximized values of  $l$ . This log likelihood ratio test is asymptotically distributed as a  $\chi^2$ -distribution with degrees of freedom equal to the difference in number of parameters.

If the environmental indicator is only observed in the selected sample, we may not estimate  $\rho_{xys}$ , say,

without further assumptions. However, if it is assumed that  $\sigma_{ys}^2$  are the same for different classes of the environmental indicator, then both  $\sigma_{xs}^2$  and  $\rho_{xys}$  may be estimated by replacing  $\sigma_{ys}^2$  with the common value in the equations.

To test if a correlation deviates from zero,  $l$  is again maximized with the corresponding correlation fixed to zero. This yields a test which is asymptotically distributed as a  $\chi^2$ -distribution with one degree of freedom.

## References

- 1 Bouchard C (ed). *The Genetics of Obesity*. CRC Press: Boca Raton, 1994.
- 2 Meyer JM, Stunkard AJ. Twin studies of human obesity. In: Bouchard C (ed). *The Genetics of Obesity*. CRC Press: Boca Raton, 1994 pp 63–78.
- 3 Sørensen TIA, Stunkard AJ. Overview of adoption studies. In: Bouchard C (ed). *The Genetics of Obesity*. CRC Press: Boca Raton, 1994, pp 49–61.
- 4 Vogler GP, Sørensen TIA, Stunkard AJ, Srinivasan MR, Rao DC. Influences of genes and shared family environment on adult body mass index assessed in an adoption study by a comprehensive path model. *Int J Obes* 1995; **19**: 40–45.
- 5 Stunkard AJ, Sørensen TIA, Hanis C, Teasdale TW, Chakraborty R, Schull WJ, Schulsinger F. An adoption study of human obesity. *N Engl J Med* 1986; **314**: 193–198.
- 6 Sørensen TIA, Price RA, Stunkard AJ, Schulsinger F. Genetics of obesity in adult adoptees and their biological siblings. *BMJ* 1989; **298**: 87–90.
- 7 Sørensen TIA, Holst C, Stunkard AJ, Skovgaard LT. Correlations of body mass index of adult adoptees and their biological and adoptive relatives. *Int J Obes* 1992; **16**: 227–236.
- 8 Kety SS, Rosenthal D, Wender PH, Schulsinger F. The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. *J Psychiatr Res* 1967/1968; **6** (Suppl 1): 345–362.
- 9 Teasdale TW, Sørensen TIA, Stunkard AJ. Genetic and early environmental components in sociodemographic influences on adult body fatness. *BMJ* 1990; **300**: 1615–1618.
- 10 Ottman R. An epidemiologic approach to gene-environment interaction. *Genet Epidemiol* 1990; **7**: 177–185.
- 11 Ottman R, Susser E, Meisner M. Control for environmental risk factors in assessing genetic effects on disease familial aggregation. *Am J Epidemiol* 1991; **134**: 298–309.
- 12 Hollander M, Wolfe DA. *Nonparametric Statistical Methods*. John Wiley and Sons: New York, 1973.
- 13 Kendler KS, Eaves LJ. Models for the joint effect of genotype and environment on liability to psychiatric illness. *Am J Psychiatr* 1986; **143**: 279–289.
- 14 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse *obese* gene and its human homologue. *Nature* 1994; **372**: 425–432.
- 15 Echwald SM, Rasmussen SB, Sørensen TIA, Andersen T, Tybjærg-Hansen A, Clausen JO, Hansen L, Hansen T, Pedersen O. Identification of two novel missense mutations in the human OB gene. *Int J Obes* 1997; **21**: 321–326.
- 16 Price RA, Stunkard AJ. Commingled analysis of obesity in twins. *Hum Hered* 1989; **39**: 121–135.
- 17 Price RA, Ness R, Sørensen TIA. Changes in commingled body mass index distributions associated with secular trends in overweight among Danish young men. *Am J Epidemiol* 1991; **133**: 501–510.
- 18 West DB, Boozer CN, Moody DL, Atkinson RL. Dietary obesity in nine inbred mouse strains. *Am J Physiol* 1992; **262**: R1025–R1032.
- 19 Heitmann BL, Lissner L, Sørensen TIA, Bengtsson C. Dietary fat intake and weight gain in women genetically predisposed for obesity. *Am J Clin Nutr* 1995; **61**: 1213–1217.

- 20 Bouchard C, Tremblay A, Després JP, Nadeau A, Lupien PJ, Thériault G, Dussault J, Moorjani S, Pinault S, Fournier G. The response to long-term overfeeding in identical twins. *N Engl J Med* 1990; **322**: 1477–1482.
- 21 Bouchard C, Tremblay A, Després JP, Thériault G, Nadeau N, Lupien PJ, Moorjani S, Prudhomme D, Fournier G. The response to exercise with constant energy intake in identical twins. *Obes Res* 1994; **2**: 400–410.
- 22 Sørensen TIA, Price RA. Secular trends in body mass index among Danish young men. *Int J Obes* 1990; **14**: 411–419.
- 23 Sonne-Holm S, Sørensen TIA, Jensen G, Schnohr P. Long-term changes of body weight in adult obese and non-obese men. *Int J Obes* 1990; **14**: 319–326.
- 24 Ravelli GP, Belmont L. Obesity in nineteen-year old men: family size and birth order associations. *Am J Epidemiol* 1979; **109**: 66–70.
- 25 Ravelli GP, Stein Z, Susser MW. Obesity in young men after famine exposure in utero and early pregnancy. *N Engl J Med* 1976; **295**: 349–353.
- 26 Allison DB, Paultre F, Heymsfield SB, Pi-Sunyer FX. Is the intra-uterine period really a critical period for the development of adiposity. *Int J Obes* 1995; **19**: 397–402.
- 27 Khosla T, Lowe CR. Obesity and smoking habits. *BMJ* 1971; **4**: 10–13.
- 28 Charney E, Goodman HG, McBride MPH, Lyon B, Pratt R. Childhood antecedent of adult obesity. Do chubby infants become obese adults? *N Engl J Med* 1976; **295**: 6–9.
- 29 Öhlin A, Rössner S. Maternal body weight development after pregnancy. *Int J Obes* 1990; **14**: 159–173.
- 30 Sørensen TIA, Holst C, Stunkard AJ. Childhood body mass index—genetic and familial environmental influences assessed in a longitudinal adoption study. *Int J Obes* 1992; **16**: 705–714.
- 31 Price RA, Cadoret RJ, Stunkard AJ, Troughton E. Genetic contributions to human fatness: an adoption study. *Am J Psychiatry* 1987; **144**: 1003–1008.
- 32 Allison DB, Heshka S, Pierson RN Jr, Wang J, Heymsfield SB. The analysis and identification of homologizer/moderator variables when the moderator is continuous: An illustration with anthropometric data. *Am J Hum Biol* 1992; **4**: 775–782.
- 33 Chakraborty R, Hanis CL. Non-random sampling in human genetics: estimation of familial correlations, model testing and interpretations. *Stat Med* 1987; **6**: 629–46.
- 34 DeMets D, Halperin M. Estimation of a simple regression coefficient in samples arising from a sub-sampling procedure. *Biometrics* 1977; **33**: 47–56.