

PEDIATRIC REVIEW

The genetic and environmental influences on childhood obesity: a systematic review of twin and adoption studies

K Silventoinen^{1,2}, B Rokholm³, J Kaprio,^{2,4,5} and TIA Sørensen³

¹Department of Sociology, Population Research Unit, University of Helsinki, Helsinki, Finland; ²Department of Public Health, University of Helsinki, Helsinki, Finland; ³Institute of Preventive Medicine, Copenhagen University Hospital, Centre for Health and Society, Copenhagen, Denmark; ⁴Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland and ⁵Institute for Molecular Medicine FIMM, Helsinki, Finland

In this systematic review, we aimed to collect together all previous twin and adoption studies on childhood and adolescent obesity up to the age of 18 years. Using several sources, we identified nine twin and five adoption studies; all of these studies had used relative weight as an indicator of obesity. Except the two twin studies from the Korean population, all studies represented Caucasian populations. In a meta-analysis of these twin studies, we found that genetic factors had a strong effect on the variation of body mass index (BMI) at all ages. The common environmental factors showed a substantial effect in mid-childhood, but this effect disappeared at adolescence. Adoption studies supported the role of family environment in childhood obesity as correlations were found between adoptees and adoptive parents; however, correlations were substantially stronger between parents and their biological offspring, further supporting the importance of genetic factors. In the future, more studies implementing genetic and environmental measures into twin models are needed as they allow estimation of the proportion of total genetic variation explained by candidate genes and analyses of gene–environment interactions. More studies of genetic architecture in non-Caucasian populations, of gene–environment interactions, and of body composition and body fat distribution are needed.

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Introduction

Childhood obesity is one of the major public health problems in the modern world. In the period 2003–2006, 32% of the US children were classified as obese or overweight,¹ and increasing trends in childhood obesity are seen all over the world.² These results are especially alarming as overweight children show a high risk of becoming obese adults.^{3,4} Childhood is an important period of life for health interventions as health-related behaviors are just in formation, and it seems possible to intervene for preventing the development of obesity.⁵ Thus, it is crucial to further understand the background mechanisms of childhood

obesity to find even more effective measures to prevent it before it begins to produce more or less irreversible health damages.

Both genetic and environmental factors will probably contribute to childhood obesity.⁶ Family studies have shown that obesity runs in families, although more detailed twin, adoption and family studies have shown that genetic differences between individuals explain a major proportion of the within-population variation in body mass index (BMI, kg m^{-2}) in adulthood.^{7–9} It is probable that genetic factors have an important role in childhood obesity also, but their role may be different or they may result from other genes than those that operate in adulthood.¹⁰ The environmental factors shared by family members, such as co-twins in twin studies, have shown only a slight effect on the variation of adult BMI.^{7,8} However, they may have a more important role in childhood, where parents and their offspring live together and where siblings obviously have a much greater opportunity to be exposed to the same environment; for

Correspondence: Dr K Silventoinen, Department of Public Health, University of Helsinki, PO Box 41, Mannerheimintie 172, Helsinki 00014, Finland.
E-mail: karri.silventoinen@helsinki.fi

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example, poor socio-economic family background has been found to be associated with the risk of obesity in children, demonstrating the importance of childhood social environment,³ and the greater role of the shared environment in childhood has also been suggested in adoption studies.⁹ The role of environmental factors in the formation of childhood obesity has important public health consequences as it may provide additional targets for effective interventions in childhood obesity.

In this systematic review, we aim to collect the evidence of the role of genetic and environmental factors on childhood obesity on the basis of existing twin, adoption and family studies. Especially, we will analyze whether the genetic architecture of obesity changes from childhood through adolescence to early adulthood.

Materials and methods

Search strategy

We aimed to find all previous family studies presenting heritability estimates of obesity in childhood. There are known Mendelian disorders resulting from single-gene mutations that cause severe obesity, which usually starts already in childhood.^{11,12} These studies are out of the scope of this review. We limited childhood period from 1 to 18 years. Studies on birth weight were not included as, because of special features of twin pregnancies, the determinants of birth weight differ between twins and singletons, and hence the heritability of birth weight is probably underestimated in twin studies.¹³ We used different sources including PubMed (www.pubmed.com), reviewing the reference lists of the found articles and searching articles that had cited the found articles using the ISI Web of Knowledge (apps.isiknowledge.com) to find relevant publications. We accepted all twin and adoption studies, but in other family studies we required a design allowing the estimation of the genetic component of variation. Because we were primarily interested in the change of the genetic architecture of obesity, we selected for further analyses only twin studies reporting age-specific results. For adoption studies such detailed studies did not exist, and thus we needed to accept all adoption studies. In the case when studies reporting correlations in BMI have been presented several times in different papers, only one paper was included. On the basis of these criteria, we found nine twin studies^{13–21} and five adoption studies,^{22–26} however, no family studies reporting heritability estimates of childhood obesity were found. In addition, we found three twin studies that had pooled information on children at different ages.^{27–29} We did not limit our search to weight, but except one early twin study,²⁷ all of these studies had used BMI or relative weight as an indicator of obesity. Two twin studies represented Korean population,^{16,19} one Taiwanese population²⁹ and one had pooled information from four East Asian populations,³⁰ but otherwise the studies were conducted in the Caucasian populations.

Methodology of twin and adoption studies

The quantitative genetic studies permit the decomposition of variation in a trait into genetic and environmental sources of variation within a population.³¹ Using twin, adoption and family studies, genetic variation can be divided into: (1) additive genetic variation, which is the sum of the effects of all alleles affecting the trait and (2) dominance genetic variation, which is caused by interaction between alleles in the same locus. Epistatic effects, which are defined as effects resulting from the interactions between alleles in different loci, are modeled as part of additive or dominance genetic effect depending on how closely the loci are linked together. Environmental variations can be distinguished into variation (3) common to relatives and (4) variation unique to each individual in the pedigree, which also will include measurement error. Epigenetic effects, if they exist, are also modeled as part of unique environmental variation. A major advantage in family studies is that they allow making assumptions on the correlations of each of these four variance components between relatives. For example, monozygotic (MZ) twins are genetically identical at the sequence level and thus the correlations of both additive and dominance genetic effects are one. Dizygotic (DZ) twins and ordinary biological siblings share, on average, half of their segregating genes and thus the expected correlation is 0.5 for additive and 0.25 for dominance genetic effects. Parents and their offspring have expected correlations of 0.5 for additive genetic effects, whereas dominance genetic effects are not correlated.³² In addition, MZ twins, DZ twins, ordinary biological siblings and adopted siblings reared in the same family have a correlation of one for common environment and zero for unique environment. When information is available only on twins reared together, the common environment and dominance genetic effects cannot be estimated simultaneously. This is because these two sources of variation affect the relative size of MZ and DZ correlations in different directions, that is, common environmental factors make DZ twins more similar whereas dominance genetic factors make them more dissimilar to MZ twins, compared with the situation when the covariance within the twin pair is totally because of additive genetic factors.

It is noteworthy that the estimation of common environmental variation is based on the comparison of MZ and DZ correlations and thus needs more power than the estimation of additive genetic variation only.³³ When the best fitting model is selected out of the set of models that fit adequately well to the data, this may lead to the rejection of common environmental component in small samples, even in the case when this effect is substantial. We have analyzed this systematically by re-estimating additive genetic, common environment and unique environment variance components based on MZ and DZ correlations in each study, regardless of whether these components are statistically significant. The estimation was performed using the Mx statistical software (Richmond, VA, USA).³⁴

After calculating the estimates for the three variance components, we conducted meta-analyses for each age group. We used a random-effects model that allows the true effects to vary around an average effect on the basis of a normal distribution. The *metan* procedure in the Stata statistical package version 9.2 (Lakeway Drive, TX, USA) was used for estimation.³⁵ All analyses showed significant heterogeneity of estimates over all ages and study samples.

The adoption studies offer another possibility to estimate the effect of genetic and environmental factors. These studies can be divided into complete and partial studies. Complete studies require that there is information on biological relatives of adoptees, allowing direct estimation of genetic effect. Partial adoption studies are based on comparisons of families with adoptees and families with biological children. These studies allow only indirect estimation of the genetic effects by comparing the differences in resemblance within adoptive and biological relatives. All adoption studies make assumptions that adoption is not selective according to the characteristics of biological parents and that the contacts between adoptees and their biological parents before or after adoption do not affect the studied trait.

The twin and adoption studies also make assumptions of random mating and lack of gene–environment co-variation, including gene–environment interactions and correlations. We will discuss in detail whether the possible violations of these assumptions may have biased previous results.

Results

The relative effects of additive genetic, common environmental and unique environmental factors with 95% confidence intervals (CI) on the variation of BMI from early childhood to the onset of adulthood are presented in Figure 1. The estimates are shown by age with separate panels for each of these three variance components. These results are based on the meta-analysis of the nine existing twin studies.^{13–21} Background information of these cohorts is presented in Appendix Table A1 and the estimates of variance components with 95% CI for each study in Appendix Table A2.

The BMI showed moderate-to-high heritability, and the additive genetic effects were statistically significant at all ages (Figure 1a). A clear age pattern was present. The heritability estimates were lowest in mid-childhood but increased in adolescence. Some decrease in heritability estimates was also found from early to mid-childhood.

The size of common environmental factors showed a reverse age pattern when compared with additive genetic factors (Figure 1b). Up to 13 years of age, common environmental factors showed an effect on BMI variation, but after that age this effect disappeared. There was a lot of variation in these estimates, but they were generally smaller

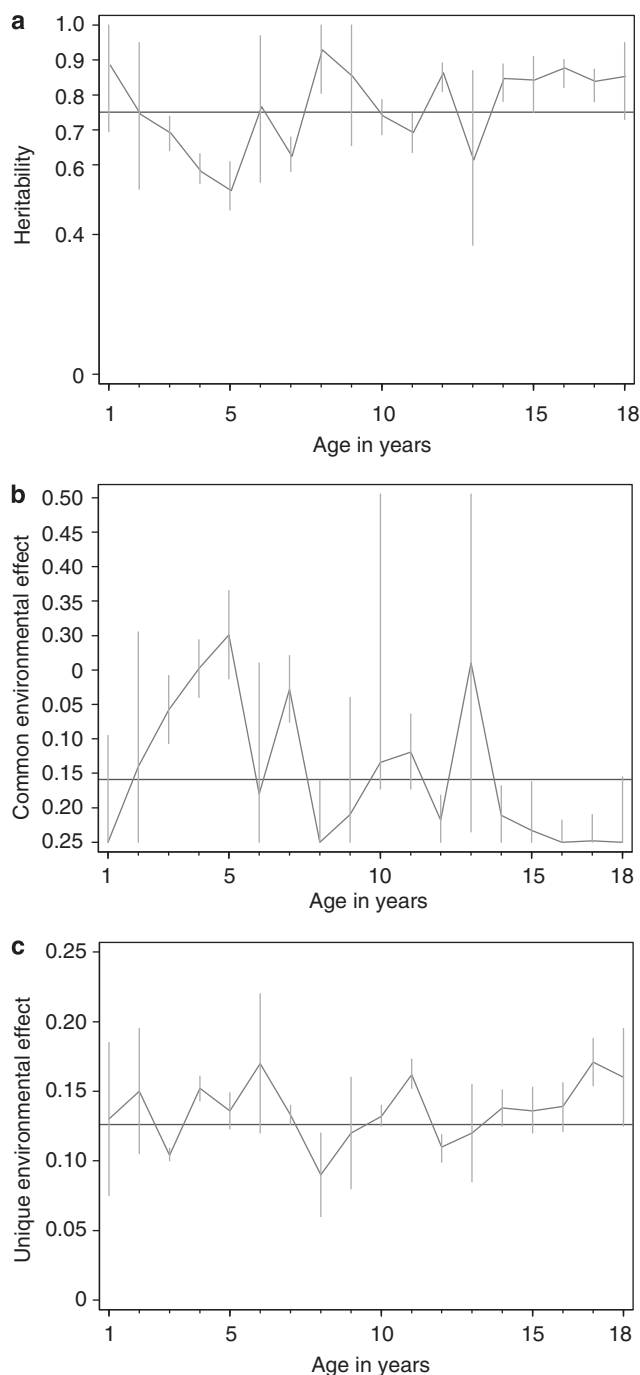


Figure 1 The age-specific estimates with their 95% confidence intervals of additive genetic factors (a), common environmental factors (b) and unique environmental factors (c) of body mass index (BMI) based on meta-analysis of published twin data (Appendix Tables 1 and 2). The horizontal line represents the overall random-effects meta-analysis estimate of heritability of BMI in childhood and adolescence.

than the estimates of additive genetic factors. The proportion of the BMI variation explained by unique environmental factors was stable over the age groups (Figure 1c).

No systematic sex or geographic differences were seen in the relative size of the variance components (Appendix Table 2). One of these twin studies also included genetic-level information, that is, genotyping of the *FTO* gene. In previous studies this candidate gene has been found to explain approximately 1% of the variation of BMI in several adult populations.^{36–38} This gene was found to be associated with BMI from 7 years of age onwards in the UK twin sample¹⁵ and a similar finding was also observed in Danish children.³⁹ However, the *FTO* gene was able to explain only a small proportion of the genetic variation of BMI in the UK study.

Table 1 summarizes information on the five existing adoption studies.^{22–26} One of these studies was a complete adoption study including information on both biological and adoptive parents of adoptees²⁶ whereas the other four studies were partial adoption studies.^{22–25} All of the adoption studies were conducted relatively early when compared with the twin studies. This is understandable as domestic adoptions have become rare in Europe and in the United States in the past two decades.

All studies that reported correlations between biological and non-biological relatives found substantial correlations between parents and their biological children as well as between biological siblings. The only statistically significant

correlations between non-biological relatives was found in a US study between mothers and their adopted children ($r=0.11$ 95% CI 0.02, 0.20).²³ It is, however, noteworthy that the similar size of correlations was found between adoptive children and their adoptive fathers ($r=0.11$ 95% CI -0.05 , 0.27) and mothers ($r=0.16$ 95% CI -0.01 , 0.31) in the UK study²² and between adoptive mothers and children ($r=0.10$ 95% CI -0.03 , 0.23) in the Danish study,²⁶ although these correlations were not statistically significant. The two US studies also reported variance components of BMI.^{23,25} The most notable feature was that the effect of unshared environment was much larger than in the existing twin studies. It is, however, not clear whether this is because of age differences between siblings or different environmental factors affecting BMI in children and their parents, or whether it reflects real differences between adoption and twin studies.

Discussion

Role of genes and environment in childhood obesity

In this systematic review of twin and adoption studies, we found clear evidence that both genetic and common

Table 1 Description of data and main results in the adoption studies of childhood obesity

References	Country, type of study	Obesity measure	Description of data	Main results (95% confidence intervals or P-values presented in brackets if reported or are countable in the study)
22	United Kingdom, partial adoption study	Weight adjusted for age and sex	142 families including 143 father-adopted children, 143 mother-adopted children, 338 father-biological son, 412 father-biological daughter, 333 mother-biological daughter and 414 mother-biological daughter pairs.	Correlations: father-adopted child 0.11 (-0.05 , 0.27), mother-adopted child 0.16 (-0.01 , 0.31), father-biological son 0.14 (0.03, 0.24), father-biological daughter 0.24 (0.15, 0.33), mother-biological son 0.19 (0.09, 0.29) and mother-biological daughter 0.19 (0.09, 0.28).
23	United States, Partial adoption study	Weight adjusted for age, sex and height	254 families with adopted or step children and 10 337 families with biological children; cross-sectional study; children were 4–11 years of age.	Additive genetic effect 0.12, common environmental effect 0.32; correlations: father-biological child 0.11 (0.09, 0.12), mother-biological child 0.10 (0.09, 0.11), father-non biological child 0.03 (-0.06 , 0.12) and mother non-biological child 0.11 (0.02, 0.20).
24	Canada, partial adoption study	Weight/height Adjusted for age and sex	374 families in Montreal including 535 adopted children, 250 biological children 374 mothers and 374 fathers; cross-sectional study; children were 1–21 years of age.	Correlations: parent-biological children 0.21 ($P=0.01$); parent-adoptive children -0.001 ($P=0.98$); biological siblings 0.37 ($P=0.001$); adopted siblings -0.03 ($P=0.76$).
25	United States, partial adoption study	BMI	241 adoptive and 245 non-adoptive families in Colorado; annual or semiannual measures.	Additive genetic effects based on sib-correlations: 0.43 at age 1, 0.53 at age 2, 0.64 at age 3, 0.52 at age 4, 0.32 at age 5, 0.39 at age 6, 0.58 at age 7 and 1.00 at age 9; heritability estimates based on parent-offspring correlations: 0.09, 0.01, 0.09, 0.37, 0.52, 0.38, 0.55, 0.38, 0.57, respectively; common environmental component was not included in the models.
26	Denmark, complete adoption study	BMI	269 adoptees and their adoptive and biological siblings and parents; annual measures from 7 to 13 years of age.	Average correlations: adoptee and biological mother 0.17 (0.03, 0.31), adoptee and biological father 0.16 (0.00, 0.32), adoptee and adoptive mother 0.10 (-0.03 , 0.23), adoptee and adoptive father 0.03 (-0.11 , 0.17); adoptee with biological siblings 0.59 (0.28, 0.90) and adoptive siblings 0.14 (-0.13 , 0.41); no systematic age patterns were found in these correlations.

BMI, body mass index.

environmental factors affect BMI variation in childhood, but the effect of common environment disappears in adolescence. This conclusion was further confirmed by a Finnish longitudinal twin study that found that the effect of common environment on BMI variation disappeared between 14 and 17 years of age.²¹ On the other hand, genetic factors had a strong effect on BMI from early childhood through adulthood. It is noteworthy that there do not seem to be any family studies in which the BMI of parents, measured when they were children, is related to the BMI of their offspring in childhood.

The common environment includes not only the effect of family background, but also, for example, the influence of common friends and other shared experiences of the co-twins. The adoption studies gave some evidence that parents' BMI may be an important factor in common environment. A similar change in genetic architecture from early childhood to the onset of adulthood has also been found in eating and physical exercise behavior. The role of common environmental factors on food preferences has been found to be substantial in young children,⁴⁰ but this effect disappears in young adulthood when eating behavior and food preferences are determined solely by additive genetic and specific environmental factors.^{41,42} Similarly, shared environmental effects are found on childhood physical activity and exercise patterns,⁴³ but weaken during adolescence⁴⁴ and are virtually absent in young adulthood.⁴⁵ The effect of childhood home environment thus seems to diminish when children become older and become more independent to make their own choices.

When studying the role of common environment using the twin design, it is noteworthy that small studies may be underpowered to detect this effect. We found that in many existing twin studies, the effect of common environment, that is, the proportion of total variance attributable to common environmental variance, was 0.30 or less. When the effect of additive genetic factors is assumed to be 0.60, it needs at least 262 twin pairs to detect a common environmental effect by a confidence level of 0.05 with a power of 80%.^{46,47} When the common environmental effect is smaller, more twin pairs are subsequently needed. Thus especially in small studies, it is crucial not to consider a statistically nonsignificant common environmental variance component as it is evident that these factors could not affect BMI variation.

It is important to note that even when genetic factors have a strong effect on childhood obesity, it does not mean that obesity would be independent of behavior. On the contrary, health behavior will probably to be an important factor behind these genetic effects. As genetic factors have a substantial effect on eating behavior and physical exercise, it is probable that genetic factors in obesity reflect not only differences in behavioral preferences, but also, for example, differences in basic metabolism. In modern developed societies where virtually no limitation to access to food exists for the large majority of

the population and where physical exercise in a large part of population is limited to leisure time, which may have a role in development of obesity, it is probable that the environmental effects show less variation between individuals and that the role of genetic factors therefore would be more important than seen in less developed societies. In the latter case, malnutrition, infections and infestations will probably also have a major role in growth and weight development.⁴⁸

Possible sources of bias in twin studies

Usually twin studies do not collect information on spouses or parents of twins, which is also the case in all above-mentioned twin studies on childhood obesity, and thus they need to make an assumption of random mating. This is, however, an unrealistic assumption as assortative mating, according to several physiological, social and psychological traits, has been well demonstrated.^{49,50} Assortative mating can be because of phenotypic assortment, referring to the preference to marry somebody with similar characteristics. This type of assortative mating may inflate heritability estimates in twin studies as it generates a correlation between spouses' genotypes and thus increases the genetic correlations within DZ twins and ordinary siblings above 0.5, as assumed in the used quantitative genetic models. This would further inflate the estimates of common environmental variance if ignored in the modeling as this estimate is based on comparison between MZ and DZ correlations under the assumption of genetic correlation of 0.5 within DZ pairs. However, it is also possible that the spousal phenotypic correlation is because of the similarities in the background environments of spouses, that is, social homogamy. For example, assortative mating by education is well established,^{51,52} and education has been found to correlate with BMI.^{53,54} Furthermore, spousal correlations in BMI may arise from shared spousal environments, when spouses form a new family unit and live in the same household, and become more similar with the duration of marriage. These latter two sources of spousal trait covariance do not violate the assumptions of twin modeling as they do not generate genetic correlation within the spouses.

When the same family environment is the main reason behind spousal correlations, they should be related to the duration of the marriage-cohabitation. However, previous studies in Norway,⁵⁵ Australia⁵⁶ and the United States⁵⁷ found that the spousal correlations of BMI were independent of the marriage duration and thus lent no support to the effect of marital environment. A previous Finnish study, using information on twins and their spouses, found that about half of the spousal correlation in BMI could be attributed to phenotypic assortment and half to social homogamy.⁵⁸ However, it is not very probable that phenotypic assortment would have greatly inflated the estimates of common environmental variation in the previous twin studies. If this would be the case, common environmental

effect should be seen in adult BMI as well, which is, however, rarely the case.^{7,8} Thus, it seems probable that common environmental effect in early childhood is a real effect and not a statistical artifact.

Another issue that needs to be analyzed in detail is how representative the twin samples are when compared with the general populations. This question was analyzed in detail in a Swedish study including measures of BMI in early adulthood in virtually the total Swedish male population based on mandatory conscription examinations.⁵⁹ This cohort included information on not only the twins participating in twin studies in Sweden, but also twins who had not participated and were thus of unknown zygosity. This study found that there was more variability in the general population for BMI than in those twins who participated in the surveys, and also the correlation of BMI within ordinary brother-pairs was lower than within DZ twin pairs. Age difference had only minimal effect on the size of correlations within brother pairs. This results in a modest overestimation of heritability of BMI when only information on participating twins was used. It is probable that this bias is related to selective participation, which has resulted in a decreased variation in twin samples. Thus, this is probably a general problem of all studies based on volunteer participation and not limited to twin studies.

The Swedish conscription study also found that MZ and DZ twins had slightly lower BMI values than singletons.⁵⁹ A similar difference was also found in twins who had not participated in the surveys, and therefore it cannot be because of selective participation. Similar difference in mean BMI between twins and singletons in late adolescence was also found in a Finnish study.⁶⁰ These differences may have their origin in prenatal conditions because compared with singleton pregnancies, twin pregnancies are characterized by earlier gestational age, lower birth weight and rapid catch-up growth, especially during the first year of life.⁶¹ This mean difference in BMI between twins and singletons is, however, not a problem in twin studies because it can be taken into account in genetic modeling.

Possible sources of bias in adoption studies

Adoption studies make a strong assumption that the correlation of adoptees with their biological parents is because of genetic factors and correlation with their adoptive parents is because of environmental factors. These assumptions may be violated when placement is selective, for example, the adoptive parents are the relatives of biological parents. In addition, it is assumed that the environment before adoption, including prenatal environment, has only a minimal effect on the studied trait and the adoptees have no contacts with biological parents after adoption. An additional issue in adoption studies is how adoptees are selected. In many cases, adoption is because of social or economical problems of the biological parents, and thus adoptees may represent low socio-economic strata of the

population. However, these assumptions seem to be fulfilled in the complete adoption study from Denmark.^{9,26}

Gene–environment interactions and correlations

So far, twin and adoption studies have usually made an assumption of the lack of gene–environment co-variation, which can be because of the gene–environment interactions or correlations. Gene–environment interaction refers to situation where the effect of environment is modified by the genotype or, the other way round, the effect of genes is modified by environment. However, it is quite probable that genes and environment do not act independently but rather interplay with each others. The early evidence from gene–environment interactions in BMI came from epidemiological studies on populations with the same genetic heritage but living in different environments and experimental studies, including MZ twin pairs.⁶ A recent Finnish twin study found that physical activity reduces genetic variance of BMI and waist circumference in early adulthood.⁴⁵ This suggests that the function of genes predisposing to obesity is suppressed in physically active persons. There is also evidence suggesting a modifying effect of physical activity on specific genes; a Danish study found that the *rs9939609* polymorphism of the *FTO* gene is associated with greater BMI in sedentary persons than in physically active persons.⁶² Similar results have also been reported in an Amish population.⁶³ The studies were cross-sectional in design and the findings therefore need confirmation in prospective studies, excluding an effect of development of obesity on physical activity.

When the gene–environment interactions are not included into the genetic models, these effects are mixed with genetic variation when co-twins share the environmental exposure, or unshared environmental variation when it is unshared. Thus, part of the genetic effect found in the previous studies may be mixed with environmental factors. These findings, when found more widely, would help reconcile why the very large genome-wide studies are unable to account for more than about 1% of the variance in BMI,^{36–38} whereas family studies find evidence for substantial heritability even when common environmental effects are allowed for.

Another mechanism that may generate covariation between genetic and environmental factors is gene–environment correlation. This refers to a situation in which environment is not independent of genotype. Gene–environment correlation can be because of a passive, active or reactive correlation.⁶⁴ In obesity, passive gene–environment correlation would be created, for example, if obese parents transfer not only their genes predisposing to obesity but also the role model to their children. Active gene–environment correlation would mean that those persons with genetic predisposition to obesity would actively seek an environment that increases obesity. For example, it was found that obese persons ate more and faster than lean persons.⁶⁵ Finally, reactive gene–environment correlation arises when obese persons create reaction from other persons

further predisposing to obesity. For example, obese persons may suffer from isolation or discrimination, which may be compensated by increased eating. In twin studies, passive gene–environment correlation increases common environmental variations, whereas active and reactive correlations increase genetic and possibly specific environmental variation. Thus, the change from passive to active gene–environment correlation is one possible explanation for the diminishing role of common environmental effects on BMI variation from childhood to adolescence.

Further prospects

In spite of the long history of family studies on childhood obesity, there are several areas of research that are only at the beginning. Both improved genotyping techniques and more complex statistical models available have greatly increased research opportunities in twin studies also. There are a lot of studies on the candidate genes of BMI, but only few of them include children.^{11,12} It would thus be important to replicate the found candidate genes in children, which may also give more insight into the biological mechanisms behind these effects. Twin studies are useful in this area as they allow estimating the proportion of the variation explained by the candidate genes of the total genetic variation. In addition to measured genetic-level information, implementing measured environmental factors into twin models would be useful as it makes analyzing gene–environment interactions possible. This would also have important public health implications as when the interplay between genes and environment shows to be important in the formation of childhood obesity, it would suggest that it is possible to affect the function of genes by changes in environmental factors, such as, but not limited to, physical exercise and diet. This would encourage health interventions in children with genetic susceptibility to obesity.

Most of the previous twin studies were conducted in Caucasian populations. However, it is questionable whether these results can be generalized to other ethnic groups. A recent twin study on the heritability of BMI and waist circumference in adolescents from eight countries found that there was more genetic variation in Caucasian than East Asian populations.³⁰ It would thus be important to analyze in detail whether the genetic architecture in East Asians and other ethnic groups is similar to the Caucasian populations. Ongoing collection of twin data in many Asian countries and from other continents will probably produce new information in this area in the near future.

General Conclusion

Genetic factors have an important effect on BMI variation, but common environmental effects are also substantial in childhood. The role of common environment, however, disappears in adolescence, probably reflecting increasing independence of children from their parents and home environment, resulting in more individualistic eating and

exercise behavior. On the other hand, growth also ends then, and teasing apart the effects of growth, which modify the relative sizes of body composition compartments from the development of obesity, that is, excess adipose tissue, requires more detailed measures than BMI. Studies on candidate genes and gene–environment interactions affecting childhood obesity or studies conducted in ethnic groups other than Caucasian are still rare, and thus these areas need to be emphasized in the future.

Conflict of interest

TIAS has the following industrial collaborations: Nestlé Research Centre, Lausanne, on obesity metabolomics (years 2003 +); Sanofi-Aventis, Denmark A/S, on health economics of obesity (years 2005 +); Coordinator of the EU FP6 project ‘Hepadip’ in which several European biotech companies participate, see www.hepadip.org (years 2005 +); DSM, The Netherlands, on obesity genomics (years 2007 +); Centre leader of the Danish Obesity Research Centre, DanORC, in which several Danish companies are affiliated, see www.danorc.dk (years 2007 +); Rambøll Management, advisor on evaluation of obesity prevention projects on Danish municipalities (years 2008 +); and Merck and Co., Inc., USA, consultant on obesity (year 2008). Other authors have no conflict of interests to declare.

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Appendix

Table A1 Characteristics of the twin cohorts and within-pair correlations for monozygotic (MZ) and dizygotic (DZ) twin pairs

References	Zygosity	Sex	Age	No. of pairs	Corr.	Mean BMI	Birth cohort	Measurement
13	MZ	M	3	1186	0.84	15.7	1986–1999	Maternal
13	DZ	M	3	1292	0.49	15.7	1986–1999	Maternal
13	MZ	F	3	1429	0.84	15.4	1986–1999	Maternal
13	DZ	F	3	1204	0.5	15.5	1986–1999	Maternal
13	DZ	OS	3	2644	0.48	—	1986–1999	Maternal
13	MZ	M	4	808	0.81	15.3	1986–1999	Maternal
13	DZ	M	4	859	0.46	15.3	1986–1999	Maternal
13	MZ	F	4	925	0.8	15	1986–1999	Maternal
13	DZ	F	4	750	0.5	15.1	1986–1999	Maternal
13	DZ	OS	4	1633	0.45	—	1986–1999	Maternal
13	MZ	M	5	474	0.79	15	1986–1999	Maternal
13	DZ	M	5	497	0.64	15	1986–1999	Maternal
13	MZ	F	5	544	0.88	14.8	1986–1999	Maternal
13	DZ	F	5	437	0.57	14.9	1986–1999	Maternal
13	DZ	OS	5	947	0.48	—	1986–1999	Maternal
13	MZ	M	7	630	0.88	15.2	1986–1999	Maternal
13	DZ	M	7	645	0.58	15.3	1986–1999	Maternal
13	MZ	F	7	738	0.88	15.3	1986–1999	Maternal
13	DZ	F	7	580	0.54	15.4	1986–1999	Maternal
13	DZ	OS	7	1200	0.55	—	1986–1999	Maternal
13	MZ	M	10	488	0.86	16.3	1986–1999	Maternal
13	DZ	M	10	425	0.56	16.3	1986–1999	Maternal
13	MZ	F	10	577	0.85	16.4	1986–1999	Maternal
13	DZ	F	10	422	0.51	16.4	1986–1999	Maternal
13	DZ	OS	10	874	0.47	—	1986–1999	Maternal
13	MZ	M	12	341	0.86	16.9	1986–1999	Maternal
13	DZ	M	12	288	0.55	17.1	1986–1999	Maternal
13	MZ	F	12	373	0.90	17.4	1986–1999	Maternal
13	DZ	F	12	279	0.49	17.5	1986–1999	Maternal
13	DZ	OS	12	554	0.51	—	1986–1999	Maternal
14	MZ	M	1	64	0.87	17.6	1973–1979	Measured
14	MZ	M	2	129	0.85	17.3	1973–1979	Measured
14	MZ	M	3	96	0.87	16.4	1973–1979	Measured
14	MZ	M	4	132	0.85	15.9	1973–1979	Measured

Table A1 (continued)

References	Zygoty	Sex	Age	No. of pairs	Corr.	Mean BMI	Birth cohort	Measurement
14	MZ	M	5	48	0.89	15.6	1973–1979	Measured
14	MZ	M	6	120	0.83	15.4	1973–1979	Measured
14	MZ	M	7	139	0.91	15.3	1973–1979	Measured
14	MZ	M	8	110	0.91	15.5	1973–1979	Measured
14	MZ	M	9	98	0.88	16	1973–1979	Measured
14	MZ	M	10	118	0.88	16.3	1973–1979	Measured
14	MZ	M	11	104	0.88	16.6	1973–1979	Measured
14	MZ	M	12	83	0.91	17.4	1973–1979	Measured
14	MZ	M	13	129	0.88	17.6	1973–1979	Measured
14	MZ	M	14	89	0.89	18.7	1973–1979	Measured
14	MZ	M	15	115	0.83	19.5	1973–1979	Measured
14	MZ	M	16	69	0.86	20.1	1973–1979	Measured
14	MZ	M	17	54	0.88	20.7	1973–1979	Measured
14	MZ	M	18	211	0.84	21.3	1973–1979	Measured
14	DZ	M	1	47	0.39	17.6	1973–1979	Measured
14	DZ	M	2	77	0.48	17.3	1973–1979	Measured
14	DZ	M	3	67	0.64	16.6	1973–1979	Measured
14	DZ	M	4	80	0.48	15.9	1973–1979	Measured
14	DZ	M	5	38	0.31	15.5	1973–1979	Measured
14	DZ	M	6	67	0.45	15.5	1973–1979	Measured
14	DZ	M	7	95	0.55	15.5	1973–1979	Measured
14	DZ	M	8	71	0.35	15.7	1973–1979	Measured
14	DZ	M	9	69	0.46	16.1	1973–1979	Measured
14	DZ	M	10	73	0.43	16.4	1973–1979	Measured
14	DZ	M	11	69	0.56	16.9	1973–1979	Measured
14	DZ	M	12	59	0.40	17.6	1973–1979	Measured
14	DZ	M	13	86	0.57	18.1	1973–1979	Measured
14	DZ	M	14	55	0.56	19.2	1973–1979	Measured
14	DZ	M	15	75	0.49	19.8	1973–1979	Measured
14	DZ	M	16	47	0.42	20.8	1973–1979	Measured
14	DZ	M	17	38	0.29	21	1973–1979	Measured
14	DZ	M	18	128	0.38	21.8	1973–1979	Measured
18	MZ	F	12	174	0.89	18.83	Ca. 1980	Measured
18	MZ	M	12	165	0.89	18.31	Ca. 1980	Measured
18	DZ	F	12	149	0.47	18.69	Ca. 1980	Measured
18	DZ	M	12	157	0.32	18.88	Ca. 1980	Measured
18	DZ	OS	12	261	0.44	18.87	Ca. 1980	Measured
18	MZ	F	14	142	0.89	20.56	Ca. 1980	Measured
18	MZ	M	14	140	0.89	19.6	Ca. 1980	Measured
18	DZ	F	14	123	0.41	20.17	Ca. 1980	Measured
18	DZ	M	14	127	0.33	20.22	Ca. 1980	Measured
18	DZ	OS	14	206	0.4	20.73	Ca. 1980	Measured
18	MZ	F	16	148	0.88	21.43	Ca. 1980	Measured
18	MZ	M	16	137	0.87	21.54	Ca. 1980	Measured
18	DZ	F	16	98	0.31	21.52	Ca. 1980	Measured
18	DZ	M	16	99	0.24	21.22	Ca. 1980	Measured
18	DZ	OS	16	204	0.29	22.57	Ca. 1980	Measured
19	MZ	M	15.5	279	0.83	20.3	1987–1993	Self-reporting
19	DZ	M	15.3	82	0.33	20.7	1987–1993	Self-reporting
19	MZ	F	15.6	319	0.88	19.8	1987–1993	Self-reporting
19	DZ	F	15.6	82	0.42	19.7	1987–1993	Self-reporting
19	DZ	OS	15.4	126	0.31	20	1987–1993	Self-reporting
15	DZ	OS	4	1010	0.54	15.79	1994–1996	Maternal
15	DZ	OS	7	819	0.45	15.75	1994–1996	Maternal
15	DZ	OS	10	950	0.45	17.26	1994–1996	Maternal
15	DZ	OS	11	1329	0.42	17.83	1994–1996	Maternal
15	DZ	M	4	555	0.62	15.79	1994–1996	Maternal
15	DZ	M	7	476	0.46	15.75	1994–1996	Maternal
15	DZ	M	10	547	0.44	17.26	1994–1996	Maternal
15	DZ	M	11	661	0.47	17.83	1994–1996	Maternal
15	DZ	F	4	595	0.59	15.79	1994–1996	Maternal
15	DZ	F	7	517	0.55	15.75	1994–1996	Maternal
15	DZ	F	10	593	0.52	17.26	1994–1996	Maternal
15	DZ	F	11	735	0.48	17.83	1994–1996	Maternal
15	MZ	M	4	638	0.85	15.84	1994–1996	Maternal
15	MZ	M	7	616	0.8	15.64	1994–1996	Maternal

Table A1 (continued)

References	Zygoty	Sex	Age	No. of pairs	Corr.	Mean BMI	Birth cohort	Measurement
15	MZ	M	10	679	0.84	17.08	1994–1996	Maternal
15	MZ	M	11	703	0.78	17.75	1994–1996	Maternal
15	MZ	F	4	784	0.85	15.84	1994–1996	Maternal
15	MZ	F	7	720	0.81	15.64	1994–1996	Maternal
15	MZ	F	10	804	0.88	17.08	1994–1996	Maternal
15	MZ	F	11	823	0.86	17.75	1994–1996	Maternal
17	MZ	Both	10.9	41	0.85	18.9	Not reported	Measured
17	DZ	Both	11	25	0.24	18.5	Not reported	Measured
20	MZ	M	16	132	0.804	20.2	1975–1979	Self-reporting
20	MZ	M	17	132	0.858	20.8	1975–1979	Self-reporting
20	DZ	M	16	167	0.363	20.5	1975–1979	Self-reporting
20	DZ	M	17	167	0.372	21.3	1975–1979	Self-reporting
20	MZ	F	16	214	0.862	20.2	1975–1979	Self-reporting
20	MZ	F	17	214	0.854	20.5	1975–1979	Self-reporting
20	DZ	F	16	181	0.392	20.3	1975–1979	Self-reporting
20	DZ	F	17	181	0.414	20.6	1975–1979	Self-reporting
20	DZ	OS	16	362	0.229	20.35	1975–1979	Self-reporting
20	DZ	OS	17	362	0.186	20.85	1975–1979	Self-reporting
16	MZ	Both	4	128	0.93	15.3	1998–2004	Maternal
16	DZ	Both	4	459	0.61	15.5	1998–2005	Maternal
21	MZ	M	11	370	0.84	17.6	1983–1987	Self-reporting
21	MZ	M	14	316	0.83	19.2	1983–1987	Self-reporting
21	MZ	M	17	282	0.80	21.5	1983–1987	Self-reporting
21	DZ	M	11	416	0.50	17.8	1983–1987	Self-reporting
21	DZ	M	14	355	0.52	19.4	1983–1987	Self-reporting
21	DZ	M	17	316	0.39	21.9	1983–1987	Self-reporting
21	MZ	F	11	377	0.79	17.5	1983–1987	Self-reporting
21	MZ	F	14	356	0.81	19.2	1983–1987	Self-reporting
21	MZ	F	17	334	0.77	20.7	1983–1987	Self-reporting
21	DZ	F	11	354	0.50	17.6	1983–1987	Self-reporting
21	DZ	F	14	330	0.49	19.5	1983–1987	Self-reporting
21	DZ	F	17	309	0.39	21.1	1983–1987	Self-reporting
21	DZ	OS	11	734	0.41	—	1983–1987	Self-reporting
21	DZ	OS	14	666	0.38	—	1983–1987	Self-reporting
21	DZ	OS	17	595	0.33	—	1983–1987	Self-reporting

Abbreviations: F, female–female pairs; M, male–male pairs; OS, opposite-sex pairs.

Table A2 Standardized estimates of additive genetic (a^2), common environmental (c^2) and specific environmental (e^2) variance components with 95% confidence intervals of childhood BMI in existing twin studies^a

Reference	Country	Sex	Age	a^2 (95% CI)	c^2 (95% CI)	e^2 (95% CI)
14	Sweden	Male	1	0.87 (0.56, 0.91)	0.00 (0.00, 0.31)	0.13 (0.09, 0.20)
14	Sweden	Male	2	0.74 (0.46, 0.88)	0.11 (0.00, 0.39)	0.15 (0.11, 0.20)
13	The Netherlands	Male	3	0.71 (0.64, 0.77)	0.20 (0.14, 0.27)	0.09 (0.09, 0.10)
13	The Netherlands	Female	3	0.68 (0.60, 0.76)	0.16 (0.08, 0.24)	0.16 (0.15, 0.17)
14	Sweden	Male	3	0.46 (0.24, 0.77)	0.41 (0.10, 0.62)	0.13 (0.09, 0.18)
13	The Netherlands	Male	4	0.70 (0.60, 0.78)	0.11 (0.03, 0.21)	0.19 (0.17, 0.21)
13	The Netherlands	Female	4	0.60 (0.50, 0.71)	0.20 (0.10, 0.29)	0.20 (0.18, 0.22)
14	Sweden	Male	4	0.74 (0.46, 0.88)	0.11 (0.00, 0.38)	0.15 (0.11, 0.20)
15	United Kingdom	Male	4	0.46 (0.37, 0.56)	0.39 (0.29, 0.48)	0.15 (0.13, 0.17)
15	United Kingdom	Female	4	0.52 (0.43, 0.62)	0.33 (0.23, 0.42)	0.15 (0.13, 0.17)
16	South Korea	Both	4	0.64 (0.53, 0.76)	0.29 (0.17, 0.39)	0.07 (0.05, 0.09)
13	The Netherlands	Male	5	0.30 (0.20, 0.41)	0.49 (0.39, 0.58)	0.21 (0.18, 0.24)
13	The Netherlands	Female	5	0.62 (0.51, 0.74)	0.26 (0.14, 0.37)	0.12 (0.11, 0.14)
14	Sweden	Male	5	0.89 (0.63, 0.93)	0.00 (0.00, 0.26)	0.11 (0.07, 0.18)
14	Sweden	Male	6	0.76 (0.45, 0.87)	0.07 (0.00, 0.38)	0.17 (0.13, 0.23)
13	The Netherlands	Male	7	0.60 (0.51, 0.70)	0.28 (0.19, 0.38)	0.12 (0.11, 0.14)
13	The Netherlands	Female	7	0.68 (0.58, 0.76)	0.20 (0.12, 0.30)	0.12 (0.11, 0.13)
14	Sweden	Male	7	0.72 (0.49, 0.93)	0.19 (0.00, 0.42)	0.09 (0.07, 0.12)
15	United Kingdom	Male	7	0.68 (0.55, 0.78)	0.12 (0.03, 0.25)	0.20 (0.18, 0.23)
15	United Kingdom	Female	7	0.52 (0.41, 0.64)	0.29 (0.17, 0.39)	0.19 (0.17, 0.21)

Table A2 (continued)

Reference	Country	Sex	Age	a^2 (95% CI)	c^2 (95% CI)	e^2 (95% CI)
14	Sweden	Male	8	0.91 (0.73, 0.94)	0.00 (0.00, 0.18)	0.09 (0.06, 0.12)
14	Sweden	Male	9	0.84 (0.54, 0.91)	0.04 (0.00, 0.34)	0.12 (0.09, 0.17)
13	The Netherlands	Male	10	0.60 (0.49, 0.73)	0.26 (0.13, 0.37)	0.14 (0.12, 0.16)
13	The Netherlands	Female	10	0.68 (0.56, 0.81)	0.17 (0.04, 0.29)	0.15 (0.13, 0.17)
14	Sweden	Male	10	0.88 (0.59, 0.91)	0.00 (0.00, 0.29)	0.12 (0.09, 0.16)
15	United Kingdom	Male	10	0.80 (0.68, 0.85)	0.04 (0.00, 0.16)	0.16 (0.14, 0.18)
15	United Kingdom	Female	10	0.72 (0.62, 0.84)	0.16 (0.05, 0.26)	0.12 (0.11, 0.13)
14	Sweden	Male	11	0.64 (0.39, 0.90)	0.24 (0.00, 0.49)	0.12 (0.09, 0.17)
15	United Kingdom	Male	11	0.62 (0.51, 0.74)	0.16 (0.04, 0.27)	0.22 (0.20, 0.25)
15	United Kingdom	Female	11	0.76 (0.66, 0.86)	0.10 (0.01, 0.20)	0.14 (0.13, 0.16)
21	Finland	Male	11	0.72 (0.55, 0.83)	0.16 (0.01, 0.29)	0.16 (0.14, 0.19)
21	Finland	Female	11	0.58 (0.43, 0.74)	0.21 (0.05, 0.35)	0.21 (0.18, 0.25)
17	Ohio, United States	Both	11	0.85 (0.54, 0.91)	0.00 (0.00, 0.31)	0.15 (0.09, 0.26)
13	The Netherlands	Male	12	0.62 (0.48, 0.77)	0.24 (0.09, 0.37)	0.14 (0.12, 0.17)
13	The Netherlands	Female	12	0.80 (0.67, 0.87)	0.10 (0.03, 0.23)	0.10 (0.09, 0.12)
14	Sweden	Male	12	0.91 (0.65, 0.94)	0.00 (0.00, 0.26)	0.09 (0.06, 0.13)
18	Australia	Female	12	0.85 (0.64, 0.91)	0.04 (0.00, 0.25)	0.11 (0.09, 0.14)
18	Australia	Male	12	0.89 (0.80, 0.91)	0.00 (0.00, 0.09)	0.11 (0.09, 0.14)
14	Sweden	Male	13	0.62 (0.39, 0.89)	0.26 (0.01, 0.49)	0.12 (0.09, 0.16)
14	Sweden	Male	14	0.66 (0.38, 0.91)	0.23 (0.00, 0.50)	0.11 (0.08, 0.16)
18	Australia	Female	14	0.89 (0.70, 0.91)	0.00 (0.00, 0.19)	0.11 (0.09, 0.14)
18	Australia	Male	14	0.89 (0.77, 0.92)	0.00 (0.00, 0.11)	0.11 (0.08, 0.14)
18	Australia	Male	14	0.89 (0.77, 0.92)	0.00 (0.00, 0.11)	0.11 (0.08, 0.14)
21	Finland	Male	14	0.62 (0.48, 0.78)	0.21 (0.06, 0.34)	0.17 (0.14, 0.20)
21	Finland	Female	14	0.64 (0.49, 0.81)	0.17 (0.00, 0.31)	0.19 (0.16, 0.22)
14	Sweden	Male	15	0.68 (0.40, 0.87)	0.15 (0.00, 0.43)	0.17 (0.13, 0.23)
19	South Korea	Male	15 $\frac{1}{2}$	0.83 (0.64, 0.86)	0.00 (0.00, 0.19)	0.17 (0.14, 0.21)
19	South Korea	Female	15 $\frac{1}{2}$	0.88 (0.63, 0.90)	0.00 (0.00, 0.25)	0.12 (0.10, 0.14)
14	Sweden	Male	16	0.86 (0.50, 0.90)	0.00 (0.00, 0.36)	0.14 (0.10, 0.21)
18	Australia	Female	16	0.88 (0.75, 0.91)	0.00 (0.00, 0.13)	0.12 (0.09, 0.16)
18	Australia	Male	16	0.87 (0.77, 0.90)	0.00 (0.00, 0.10)	0.13 (0.10, 0.17)
20	Finland	Male	16	0.80 (0.62, 0.85)	0.00 (0.00, 0.17)	0.20 (0.15, 0.26)
20	Finland	Female	16	0.86 (0.71, 0.89)	0.00 (0.00, 0.15)	0.14 (0.11, 0.17)
20	Finland	Male	17	0.86 (0.71, 0.89)	0.00 (0.00, 0.14)	0.14 (0.11, 0.19)
20	Finland	Female	17	0.85 (0.67, 0.88)	0.00 (0.00, 0.18)	0.15 (0.12, 0.18)
21	Finland	Male	17	0.80 (0.64, 0.83)	0.00 (0.00, 0.15)	0.20 (0.17, 0.24)
21	Finland	Female	17	0.76 (0.58, 0.80)	0.01 (0.00, 0.18)	0.23 (0.19, 0.27)
14	Sweden	Male	17	0.88 (0.63, 0.92)	0.00 (0.00, 0.25)	0.12 (0.08, 0.19)
14	Sweden	Male	18	0.84 (0.65, 0.87)	0.00 (0.00, 0.19)	0.16 (0.13, 0.20)

^aThe variance components are re-estimated using published within-pair correlations of body mass index (BMI).