Genetic epidemiology of obesity and nutrition

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Content of lecture

- Introduction
- Genetics of obesity
  - Family studies
  - Molecular genetic studies
- Genetics of obesity risk factors
- Gene-environment interactions in obesity
- Further issues in the genetics of obesity
Family studies
Gregory Mendel

- 1822-1884
- Crossing experiments using peas
- Showed that (monogenetic) traits can be inherited between generations by a certain pattern
- Rediscovered in 1900
Familial clustering of disease
Consider locus with alleles $a$ and $A$
Genotypic effects on phenotype measured in terms of ‘$a$’ and ‘$d$’
‘$a$’ is additive genotypic effect, ‘$d$’ is effect due to dominance

Example: mean effect of Apo E3/3 vs E4/4 on cholesterol levels

Genotypic effects over all relevant loci can be summed
Hereditary pattern of quantitative traits seems to be different than in traits regulated by only one gene.

Dispute at the beginning of the 20th century.

However the background pattern of heritability does not differ.

It can be shown that if the trait is caused by the effect of several genes, the distribution of the trait is normal.

Proofed mathematically by Ronald Fisher (1890-1962) whose paper in 1918 created the base for statistical genetics.

- Calculated expected genetic correlations between different types of relatives.

(MR. received June 6, 1918. Read July 8, 1918. Lancelot separately October 1, 1918.)

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Several attempts have already been made to interpret the well-established results of biometry in accordance with the Mendelian scheme of inheritance. It is here attempted to ascertain the biometrical properties of a population of a more general type than has hitherto been examined, inheritance in which follows this scheme. It is hoped that in this way it will be possible to make a more exact analysis of the causes of human variability. The great body of available statistics show us that the deviations of a human measurement from its mean follow very closely the Normal Law of Errors, and, therefore, that the variability may be uniformly measured by the standard deviation corresponding to the square root of the mean square error. When there are two independent causes of variability capable of producing in an otherwise uniform population distributions with standard deviations \( \sigma_x \) and \( \sigma_y \), it is found that the distribution, when both causes act together, has a standard deviation \( \sqrt{\sigma_x^2 + \sigma_y^2} \). It is therefore desirable in analysing the causes of variability to deal with the square of the standard deviation as the measure of variability. We shall term this quantity the Variance of the normal population to which it refers, and we may now ascribe to the constituent causes fractions or percentages of the total variance which they together produce. It is desirable on the one hand that the elementary ideas at the basis of the calculus of correlations should be clearly understood, and easily expressed in ordinary language, and on the other that loose phrases about the "percentage of causation,"
Sources of human variation

- Some of the traits showing variation in humans are determinate purely by genes
  - For example eye or hair color
- Most of quantitative traits are, however, affected by both environmental and genetic factors
- It is noteworthy that at an individual level, it makes no sense to separate the effects of genes and environment since they both act simultaneously
- For example human growth is regulated by genes, but it needs also nutrients
- Thus it cannot be said that part of adult stature is generated by genes and part by environment
- However at a population level, we can say that part of the differences in height within population is caused by genetic and part by environmental differences between individuals
Genetic variation

Environmental variation
Components of variation

- **Additive genetic variation (A)**
  - Additive effect of alleles over all relevant loci
  - Inherited from parents to offspring

- **Dominance genetic variation (D)**
  - Dominance of one allele over its pair (dominance)
  - Interaction between different loci (epistasis)
  - Genetic effect because of reshuffling of genes in offspring

- **Common environmental variation (C)**
  - All environmental factors which make family members similar

- **Specific environmental variation (E)**
  - All environmental factors which make individuals dissimilar
  - Epigenetic heritability
  - Measurement error is included in this part of variation in simple models
Dividing genetic and environmental variation

- Separating genetic variation from environmental variation is not possible if only information on unrelated individuals is available.
- It requires a priori information on how much genetic and environmental variation individuals share.
  - In animal experiments, this can be done easily (mice, fruit flies etc.).
- In human genetics, where experimental designs cannot be used, it is possible to use natural experiments.
  - These designs need certain assumptions and it needs to be considered how realistic they are.
- Adoption, family and twin designs.
Adoption design

- Adoption design is the most straightforward way to separate genetic and environmental variations.
- It is based on the assumption that adopted children share their genes (additive genetic variation) only with their biological parents and environmental influences only with their adoptive parents.
- Thus correlation of adoptive children with their biological parents (or biological siblings) would indicate the effect of genetic factors.
- Correspondingly correlation with adoptive parents or siblings in their new family suggests the effect of environmental factors.
Table 1. Body-Mass Index and Intrapair Correlations in Monozygotic and Dizygotic Pairs of Twins Reared Apart or Together.*

<table>
<thead>
<tr>
<th>TYPE</th>
<th>MEN</th>
<th>WOMEN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO.</td>
<td>BODY-</td>
</tr>
<tr>
<td></td>
<td>OF</td>
<td>MASS</td>
</tr>
<tr>
<td>Monozygotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reared apart</td>
<td>49</td>
<td>24.8 ± 2.4</td>
</tr>
<tr>
<td>Reared together</td>
<td>66</td>
<td>24.2 ± 2.9</td>
</tr>
<tr>
<td>Dizygotic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reared apart</td>
<td>75</td>
<td>25.1 ± 3.0</td>
</tr>
<tr>
<td>Reared together</td>
<td>89</td>
<td>24.6 ± 2.7</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD.

Figure 1. Genetic and Environmental Components of Variance in Body-Mass Index. The contributions of shared and correlated environments each account for less than 1 percent of the variance among men and women.
Problems in adoption studies

- Historically the adoption design has produced very important results
  - For example genetics of schizophrenia
- There are, however, also certain problems in this design
- It makes a strong assumption that correlation with biological parents is because of shared genetic factors
- However environment during pregnancy and early childhood may also have influence
  - For example, exposition to nicotine because of maternal smoking
- Also if adoptive parents are relatives of biological parents, it creates genetic correlation between them and adoptees
- It is also worth noting that adoptive parents are very highly motivated and carefully selected
  - Decreases environmental variation and can thus underestimate the effect of environmental factors
Nowadays adoptions have become increasingly rear and selective
Many adoptions have also done after early childhood and contacts with biological parents are encouraged
Thus especially domestic adoption studies have become very difficult in most of industrialized countries
However increasing rates of international adoptions create an interesting study design
Children with different ethnicity living in the same environment
  ◦ Rare opportunity to analyze the effect of genetic and environmental factors on differences between groups
Systolic blood pressure at 18 years of age in native born Swedish and international adoptees to Sweden

ONLY MEN

Silventoinen et al 2010, J Hypertens
Family design

- If information available only on siblings, common environmental and genetic factors cannot be separated
  - Familial effect
  - Sometimes a sufficient design
- However, if information available also on extended families (cousins, aunts/uncles etc.), it is possible to separate genetic and environmental influences
  - This design was used by Fisher in 1918
- Environmental effects
  - Can we expect that cousins do not share any environmental variation?
- Age effect is sometimes problematic
  - Children and adults in the same data
  - Partly different genes affect at different ages in many traits
  - Leads to lower heritability estimates
Figure 1  Pedigree illustrating the non-biological relationships used in the analyses. Mother (circle) has one son (lower leftmost square) with one father (top leftmost square), then remarries (top rightmost square) and has another son (lower rightmost square). Solid arrows indicate the ‘quasi father–son’ relation and the dotted arrow indicates the ‘father 1–father 2’ relation.

Table 3  Pearson correlation coefficients ($r$) for BMI among various types of family pairs

<table>
<thead>
<tr>
<th>Relation</th>
<th>Type of family</th>
<th>No. of pairs</th>
<th>$r$</th>
<th>95% CI</th>
<th>$P &lt;^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biological relations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-brothers</td>
<td>1M, 1F, 2S</td>
<td>74 674</td>
<td>0.36</td>
<td>0.35–0.37</td>
<td>0.0001</td>
</tr>
<tr>
<td>Maternal half-brothers</td>
<td>1M, 2F, 2S</td>
<td>4164</td>
<td>0.21</td>
<td>0.18–0.24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Paternal half-brothers</td>
<td>2M, 1F, 2S</td>
<td>4337</td>
<td>0.11</td>
<td>0.08–0.14</td>
<td>0.0001</td>
</tr>
<tr>
<td>Father–first son</td>
<td>1M, 1F, 2S</td>
<td>8650</td>
<td>0.29</td>
<td>0.27–0.31</td>
<td>0.0001</td>
</tr>
<tr>
<td>Father–last son</td>
<td>1M, 1F, 2S</td>
<td>8650</td>
<td>0.28</td>
<td>0.26–0.30</td>
<td>0.0001</td>
</tr>
<tr>
<td>Father–son</td>
<td>Any</td>
<td>22 517</td>
<td>0.28</td>
<td>0.27–0.29</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Non-biological quasi relations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father1–father2</td>
<td>1M, 2F</td>
<td>362</td>
<td>0.08</td>
<td>−0.02–0.18</td>
<td>0.1479</td>
</tr>
<tr>
<td>Quasi father–son</td>
<td>1M, 2F, 2S</td>
<td>1576</td>
<td>0.06</td>
<td>0.01–0.11</td>
<td>0.0143</td>
</tr>
</tbody>
</table>

$^a$M = mothers; F = fathers; S = sons. $^b$Probability $H_0$: $r = 0$. $^c$See Figure 1.
Twin design

- Twin design has been (and still is) the most important way to analyze genetic and environmental influences in human genetics.
- It is based on a simple principle that when MZ twins share the same gene sequence DZ twins share, on average, 50% or their segregating genes.
  - Epigenetic factors can be interpreted as part of environmental variation.
- Rapid methodological development during the last two decades has vastly increased opportunities in twin research.
  - For example, analyses of developmental processes and correlations between multiple traits.
Decomposing human variation

- Principles of twin analyses were created already at the beginning of the 20th century
  - Ronald Fisher 1918
- The simplest way is to compare MZ and DZ correlations
  - For example: $a^2 = 2(r_{MZ} - r_{DZ})$
- However this method has many limitations and it has not been used at least for two decades
- In modern twin research, variance components are estimated using linear structural equation modeling
  - They are thus interpreted as latent variance components lying behind the observed trait variation
  - Also regression based methods are available
- Twin design allows to determinate a priory genetic and environmental correlations within MZ and DZ twin pairs
- Usually common environmental and dominant genetic factors cannot be estimated simultaneously
Genetic twin model for one trait

\[
\begin{align*}
A & \quad C & \quad E \\
1 & \quad 1/0.5 & \quad 1 \\
1 & \quad 1 & \quad 1 \\
1 & \quad 1 & \quad 1 \\
\end{align*}
\]

IQ_{TWIN1} 

IQ_{TWIN2}
Heritability of BMI from 1 to 18 years of age: a meta-analysis of eight twin studies

Silventoinen et al., Int J Obes 2009
Change of heritability of BMI in Finland from 11 to 17 years of age

Boys

Girls

Lajunen et al., Int J Obes, 2009
Silventoinen et al., Am J Clin Nutr, 2009
Population 128 million
National Gross Product per capita US$32,840
Life expectancy at birth 79 y in men and 86 y in women
23% overweight (BMI ≥ 25 kg/m²)
Source: WHO
Karri Silventoinen
University of Helsinki

Yoshie Yokoyama
Osaka City University
Heritability of BMI in Japanese children from two to 11 years of age

Silventoinen et al., Behavior Genetics, 2011
Simplex-model for the change of BMI

Silventoinen at al, Behavior Genetics, 2011
Simplex-model continue

Silventoinen at al, Behavior Genetics, 2011
Genetics of BMI in Caucasian and Japanese populations

- Most of the variation of BMI is explained by genetic factors.
- Common environmental factors affect BMI in childhood, but their effect seems to disappear at the latest in adolescence.
  - Children get more independence and can make own choices in food consumption/physical exercise.
- In the Japanese population, the genetics of BMI seems to be very similar than found previously in Caucasian populations.
  - Interesting when taking into account large ethnic and environmental differences.
- The genetic architecture of the development of BMI shows similar patter than also in other populations.
  - Strong genetic continuity over childhood.
  - However also new genetic variation starts to affect at each age.
Molecular genetic studies of obesity
Finding genetic determinants

- Candidate gene studies are useful for finding Mendelian diseases
  - In principle, hypothesis driven (in practice usually not)
  - Huge multiple testing problem mainly because of publication bias

- Linkage studies
  - Analyzing genetic markers (tandem repeats, tagSNPs) identity by descent (IBD) in families
  - Multiple testing are taken into account when calculating LODs (log of p-values)
  - Still useful especially when studying large pedigrees

- Candidate gene and linkage studies can found only genes with strong effect sizes (=high penetrance)
  - Results very modest for complex traits except some rare monogenic disorders
  - Problems to replicate results

- Genom-wide association studies (GWAS)
  - Can found common alleles with moderate effect size
  - More successful when studying complex traits
Atlas of susceptibility

Penetrance
- High
- Intermediate
- Modest
- Low

Allele frequency
- Very rare
- Rare
- Uncommon
- Common

- rare alleles causing Mendelian disease
- Low-frequency variants with intermediate penetrance
- rare variants of small effect very hard to identify by genetic means
- rare examples of high-penetrance common variants influencing common disease
- most common variants implicated in common disease by GWA
Fig. 3. Relationship between the number of loci identified and the stage-1 sample size across the four waves of GWAS for BMI (panel a), and increase in number of BMI loci identified (left axis) and increase in explained BMI variance (right axis) from wave 1 through wave 4 (panel b).
Loos R, Best Pract Res Clin Endocrinol Metab, 2012
So far molecular genetics of quantitative traits has been largely disappointing except rare monogenetic mutations.

Heritability of BMI about 80% but still the known candidate genes explain less than 2% of the variation.

This may just tell that genetics is much more difficult than previously believed.

For example both gene-gene and gene-environment interactions are probably important but not sufficiently taken into account so far.

Information on genes tells hardly anything on susceptibility for obesity:

- Commercial gene tests for obesity are available but are quite useless.
- Best genetic test is information on relatives!
Genetics of obesity risk factors
Table 3
Estimates of proportional influences of additive genetic effects ($a^2$) and unshared environmental effects ($e^2$) on use of 24 food items with no sex-specific genetic effects allowed in the model

<table>
<thead>
<tr>
<th>Food item</th>
<th>Males</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$a^2$</td>
<td>CI 95%</td>
<td>$e^2$</td>
<td>CI 95%</td>
<td>$a^2$</td>
<td>CI 95%</td>
<td>$e^2$</td>
</tr>
<tr>
<td>Cooked or mashed potatoes</td>
<td>0.46</td>
<td>(0.35–0.55)</td>
<td>0.54</td>
<td>(0.45–0.65)</td>
<td>0.44</td>
<td>(0.35–0.53)</td>
<td>0.56</td>
</tr>
<tr>
<td>Fried potatoes or French fries</td>
<td>0.40</td>
<td>(0.25–0.53)</td>
<td>0.60</td>
<td>(0.47–0.75)</td>
<td>0.38</td>
<td>(0.26–0.49)</td>
<td>0.62</td>
</tr>
<tr>
<td>Rice or pasta</td>
<td>0.49</td>
<td>(0.38–0.60)</td>
<td>0.51</td>
<td>(0.40–0.62)</td>
<td>0.40</td>
<td>(0.30–0.50)</td>
<td>0.60</td>
</tr>
<tr>
<td>Porridge, muesli, cereals</td>
<td>0.42</td>
<td>(0.31–0.52)</td>
<td>0.58</td>
<td>(0.48–0.69)</td>
<td>0.41</td>
<td>(0.32–0.49)</td>
<td>0.59</td>
</tr>
<tr>
<td>Yoghurt</td>
<td>0.48</td>
<td>(0.38–0.57)</td>
<td>0.52</td>
<td>(0.43–0.62)</td>
<td>0.37</td>
<td>(0.29–0.45)</td>
<td>0.63</td>
</tr>
<tr>
<td>Reduced-fat cheeses</td>
<td>0.46</td>
<td>(0.36–0.56)</td>
<td>0.54</td>
<td>(0.44–0.64)</td>
<td>0.43</td>
<td>(0.34–0.50)</td>
<td>0.57</td>
</tr>
<tr>
<td>Other cheeses&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.38</td>
<td>(0.27–0.48)</td>
<td>0.62</td>
<td>(0.52–0.73)</td>
<td>0.37</td>
<td>(0.29–0.45)</td>
<td>0.63</td>
</tr>
<tr>
<td>Fish</td>
<td>0.45</td>
<td>(0.32–0.56)</td>
<td>0.55</td>
<td>(0.44–0.53)</td>
<td>0.44</td>
<td>(0.33–0.53)</td>
<td>0.57</td>
</tr>
<tr>
<td>Chicken, turkey</td>
<td>0.47</td>
<td>(0.36–0.57)</td>
<td>0.53</td>
<td>(0.43–0.64)</td>
<td>0.49</td>
<td>(0.40–0.57)</td>
<td>0.51</td>
</tr>
<tr>
<td>Meat</td>
<td>0.22</td>
<td>(0.11–0.32)</td>
<td>0.78</td>
<td>(0.68–0.89)</td>
<td>0.44</td>
<td>(0.35–0.52)</td>
<td>0.56</td>
</tr>
<tr>
<td>Sausage</td>
<td>0.40</td>
<td>(0.30–0.49)</td>
<td>0.60</td>
<td>(0.51–0.70)</td>
<td>0.46</td>
<td>(0.39–0.53)</td>
<td>0.54</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.30</td>
<td>(0.16–0.44)</td>
<td>0.70</td>
<td>(0.56–0.84)</td>
<td>0.37</td>
<td>(0.25–0.48)</td>
<td>0.63</td>
</tr>
<tr>
<td>Fresh vegetables&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.40</td>
<td>(0.30–0.50)</td>
<td>0.60</td>
<td>(0.50–0.70)</td>
<td>0.48</td>
<td>(0.39–0.55)</td>
<td>0.52</td>
</tr>
<tr>
<td>Cooked vegetables</td>
<td>0.38</td>
<td>(0.27–0.48)</td>
<td>0.62</td>
<td>(0.52–0.73)</td>
<td>0.50</td>
<td>(0.41–0.57)</td>
<td>0.50</td>
</tr>
<tr>
<td>Fruits&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.51</td>
<td>(0.40–0.60)</td>
<td>0.49</td>
<td>(0.40–0.60)</td>
<td>0.49</td>
<td>(0.41–0.56)</td>
<td>0.51</td>
</tr>
<tr>
<td>Berries</td>
<td>0.37</td>
<td>(0.25–0.49)</td>
<td>0.63</td>
<td>(0.51–0.75)</td>
<td>0.44</td>
<td>(0.35–0.53)</td>
<td>0.56</td>
</tr>
<tr>
<td>Sweet desserts</td>
<td>0.23</td>
<td>(0.17–0.41)</td>
<td>0.71</td>
<td>(0.59–0.84)</td>
<td>0.33</td>
<td>(0.23–0.43)</td>
<td>0.67</td>
</tr>
<tr>
<td>Chocolate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.37</td>
<td>(0.23–0.50)</td>
<td>0.63</td>
<td>(0.30–0.77)</td>
<td>0.38</td>
<td>(0.27–0.48)</td>
<td>0.62</td>
</tr>
<tr>
<td>Other sweets&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.55</td>
<td>(0.40–0.68)</td>
<td>0.45</td>
<td>(0.32–0.60)</td>
<td>0.54</td>
<td>(0.42–0.60)</td>
<td>0.46</td>
</tr>
<tr>
<td>Salty snacks</td>
<td>0.43</td>
<td>(0.28–0.56)</td>
<td>0.57</td>
<td>(0.44–0.72)</td>
<td>0.41</td>
<td>(0.29–0.52)</td>
<td>0.59</td>
</tr>
<tr>
<td>Pizza</td>
<td>0.34</td>
<td>(0.18–0.49)</td>
<td>0.66</td>
<td>(0.51–0.82)</td>
<td>0.47</td>
<td>(0.28–0.63)</td>
<td>0.53</td>
</tr>
<tr>
<td>Hamburgers&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.55</td>
<td>(0.41–0.68)</td>
<td>0.45</td>
<td>(0.32–0.60)</td>
<td>0.54</td>
<td>(0.42–0.64)</td>
<td>0.46</td>
</tr>
<tr>
<td>Fried foods</td>
<td>0.22</td>
<td>(0.09–0.34)</td>
<td>0.78</td>
<td>(0.66–0.91)</td>
<td>0.43</td>
<td>(0.32–0.52)</td>
<td>0.57</td>
</tr>
<tr>
<td>Creamy foods</td>
<td>0.36</td>
<td>(0.22–0.49)</td>
<td>0.64</td>
<td>(0.51–0.78)</td>
<td>0.29</td>
<td>(0.18–0.39)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

<sup>a</sup> Allowing sex-specific genetic effects would provide a better model fit.

<sup>b</sup> ACE model would provide a better fit for females.

<sup>c</sup> ACE model would provide a better fit for males.
Heritability of physical activity

<table>
<thead>
<tr>
<th>Country</th>
<th>A (95% CI)</th>
<th>C (95% CI)</th>
<th>E (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (males)</td>
<td>22.9 (0.0, 56.1)</td>
<td>20.6 (0.0, 46.1)</td>
<td>56.6 (43.7, 70.0)</td>
</tr>
<tr>
<td>Australia (females)</td>
<td>31.1 (0.3, 55.6)</td>
<td>16.4 (0.0, 40.1)</td>
<td>52.5 (44.0, 61.6)</td>
</tr>
<tr>
<td>Denmark (males)</td>
<td>44.4 (24.2, 55.7)</td>
<td>4.7 (0.0, 20.5)</td>
<td>51.0 (44.3, 58.2)</td>
</tr>
<tr>
<td>Denmark (females)</td>
<td>50.1 (30.3, 57.7)</td>
<td>3.1 (0.0, 19.9)</td>
<td>46.8 (40.7, 53.4)</td>
</tr>
<tr>
<td>Finland (males)</td>
<td>55.8 (38.4, 63.3)</td>
<td>6.2 (0.0, 19.3)</td>
<td>38.0 (32.0, 44.6)</td>
</tr>
<tr>
<td>Finland (females)</td>
<td>61.0 (44.5, 66.3)</td>
<td>0.0 (0.0, 13.0)</td>
<td>39.0 (33.8, 45.2)</td>
</tr>
<tr>
<td>Netherlands (males)</td>
<td>68.1 (34.2, 79.0)</td>
<td>2.7 (0.0, 35.3)</td>
<td>29.2 (21.0, 39.2)</td>
</tr>
<tr>
<td>Netherlands (females)</td>
<td>50.3 (21.3, 70.3)</td>
<td>13.3 (0.0, 38.8)</td>
<td>36.5 (29.5, 44.4)</td>
</tr>
<tr>
<td>Norway (males)</td>
<td>33.6 (6.7, 61.7)</td>
<td>31.1 (6.5, 53.4)</td>
<td>35.4 (27.6, 44.3)</td>
</tr>
<tr>
<td>Norway (females)</td>
<td>56.6 (46.5, 63.8)</td>
<td>0.0 (0.0, 14.4)</td>
<td>43.4 (36.2, 51.2)</td>
</tr>
<tr>
<td>Sweden (males)</td>
<td>63.9 (52.1, 68.6)</td>
<td>0.0 (0.0, 0.0)</td>
<td>36.1 (31.4, 41.2)</td>
</tr>
<tr>
<td>Sweden (females)</td>
<td>59.5 (46.9, 64.7)</td>
<td>0.0 (0.0, 0.0)</td>
<td>40.5 (35.3, 46.1)</td>
</tr>
<tr>
<td>UK (females)</td>
<td>70.5 (24.0, 82.3)</td>
<td>0.0 (0.0, 0.0)</td>
<td>29.5 (17.7, 46.6)</td>
</tr>
</tbody>
</table>

Stubbe JH et al., PLoSOne 2006
Genetics of obesity and environment

- Effect of environment on obesity thus cannot be separated from genetic effects
- Many genes predisposing to obesity probably actually affect through behavior
- This can explain why heritability of BMI remains high at the same time when the prevalence of obesity has dramatically increased
- Obesogenic environment can even increase heritability of BMI because there are more opportunities for different types of behavior
- For example, genes affecting likability of high fat food does not matter if this type of food is not available
Gene-environment interactions
Gene-environment interaction model for twins

\[ M + \beta_M M \]

\[ \mu + \beta_M M \]

\[ a + \beta_X M \]

\[ c + \beta_Y M \]

\[ e + \beta_Z M \]

\[ T \]
Heritability of obesity measures as a function of physical activity

Silventoinen et al., Am J Clin Nutr 2009
FTO-gene and BMI/WC

Interaction between FTO-gene and physical activity

Vimaleswaran et al, Am J Clin Nutr 2009
The difference in the BMI-increasing effect of the risk alleles of FTO-gene between physically active and inactive individuals: -0.14 kg/m² (95% CI -0.23, -0.04)

Kilpeläinen et al., PLoS Medicine, 2012
Ahmad et al.,
PLoS Genet, 2013

Figure 2. Association between the GRS and BMI in the inactive and ‘combined active’ groups (N=111,421). Physical activity was estimated according to the Cambridge Physical Activity Index (CPAI), where the inactive group is defined as individuals with a CPAI of 1 and the ‘combined active’ group as individuals with a CPAI of 2–4.
doi:10.1371/journal.pgen.1003607.g002
During the last five years (2009-2013), our understanding on the effect of physical activity on the function of genes predisposing to obesity has dramatically increased.

First it was shown that physical activity decreases genetic variation when using twin design.
- Four twin data sets in three countries (Denmark, Finland and USA)

Second it was found that the FTO gene was more strongly associated with BMI in sedentary persons as compared to physically active persons.
- This was found in several populations

Third it was found that physical activity decreases the effect of genetic risk score of 12 well replicated candidate genes for obesity in a large meta-analysis.
Further issues in the genetics of obesity (and other complex traits)

- Missing heritability
  - Why the known candidate genes explain only a fraction of genetic variation in BMI?
  - Gene-gene interactions, gene-environment interactions, genes with small effects sizes, something else?

- Gene-environment interactions
  - Interaction with physical activity
  - Are there similar interactions with nutrition or other environmental factors affecting obesity?
  - How obesogenic environment affect genetic variation of obesity?

- Epigenetics
  - How obesity affects gene-expression?
  - How differences in gene-expression predispose to obesity?