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Interplay between genes and environment

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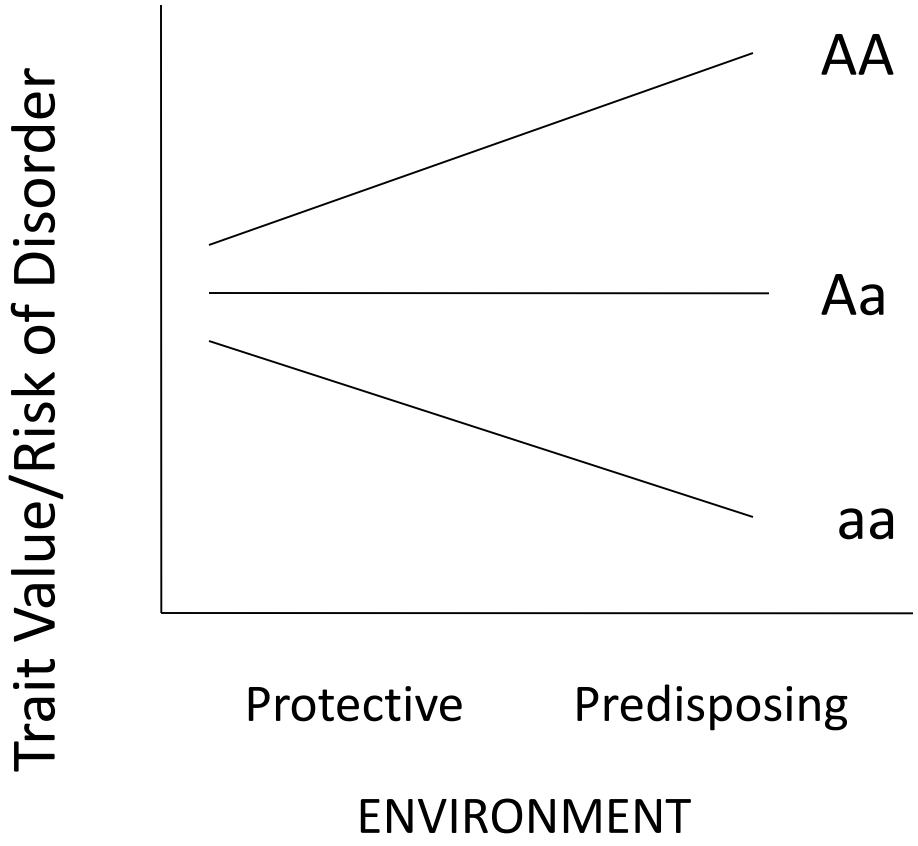
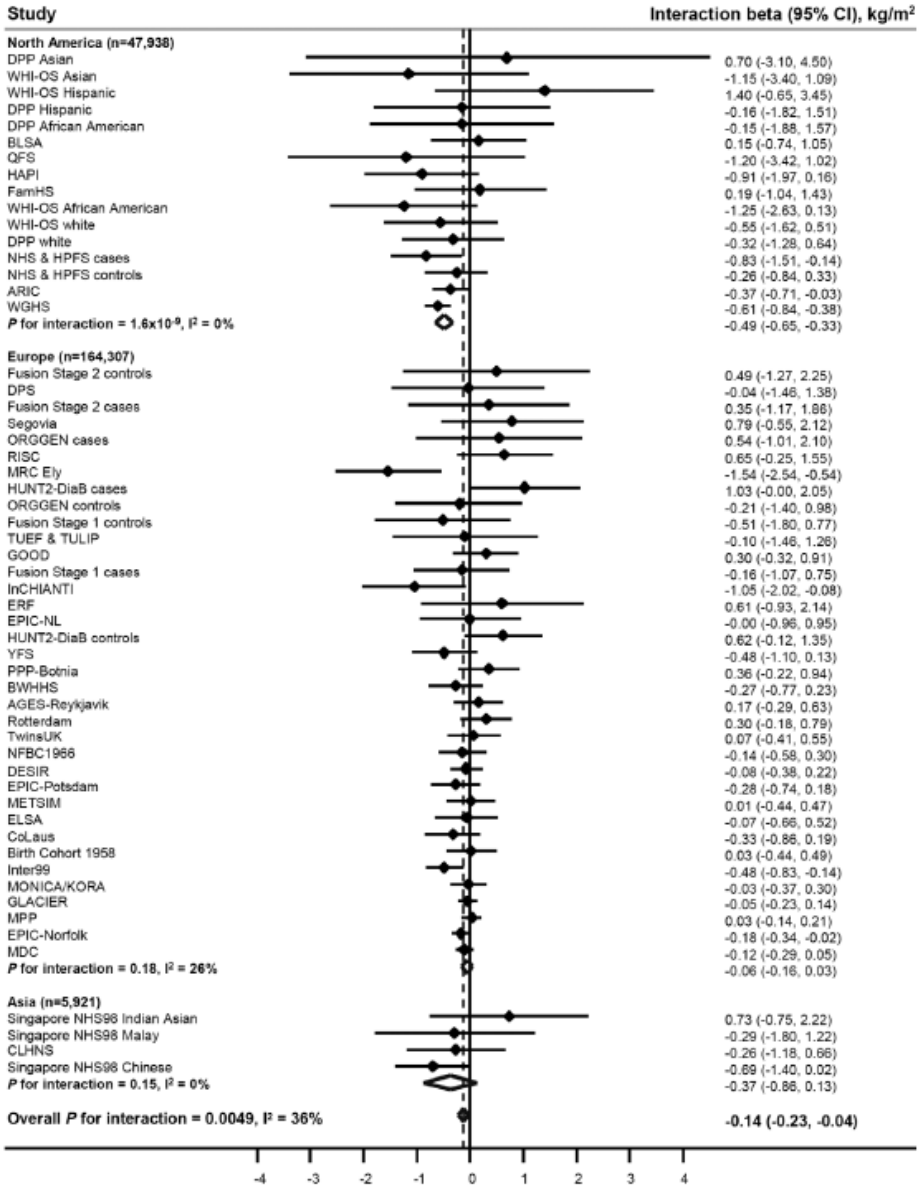
Interplay between genes and environment

- Until recently the effects of genes and environment are usually treated independently in human genetics
- It is, however, very likely that genes and environment do not operate independently but rather interact with each other
- In gene–environment interactions, the effect of same gene differs between different environments or genes modify the effect of environmental exposure
  - In practice, these two mechanisms cannot usually be distinguished
- In recent years, interest in gene–environment interactions has dramatically increased because of pharmacogenetics
  - The responses of drugs may be modified by genotype
  - Understanding these interactions may lead to personalized medicine in the future

Conceptualizing G*E interaction in the case of single gene with two alleles





Interaction between physical activity and rs9939609 FTO variant variant when predicting BMI : a meta-analysis of 218,166 adults

Kilpeläinen et al PLoS Med 2011

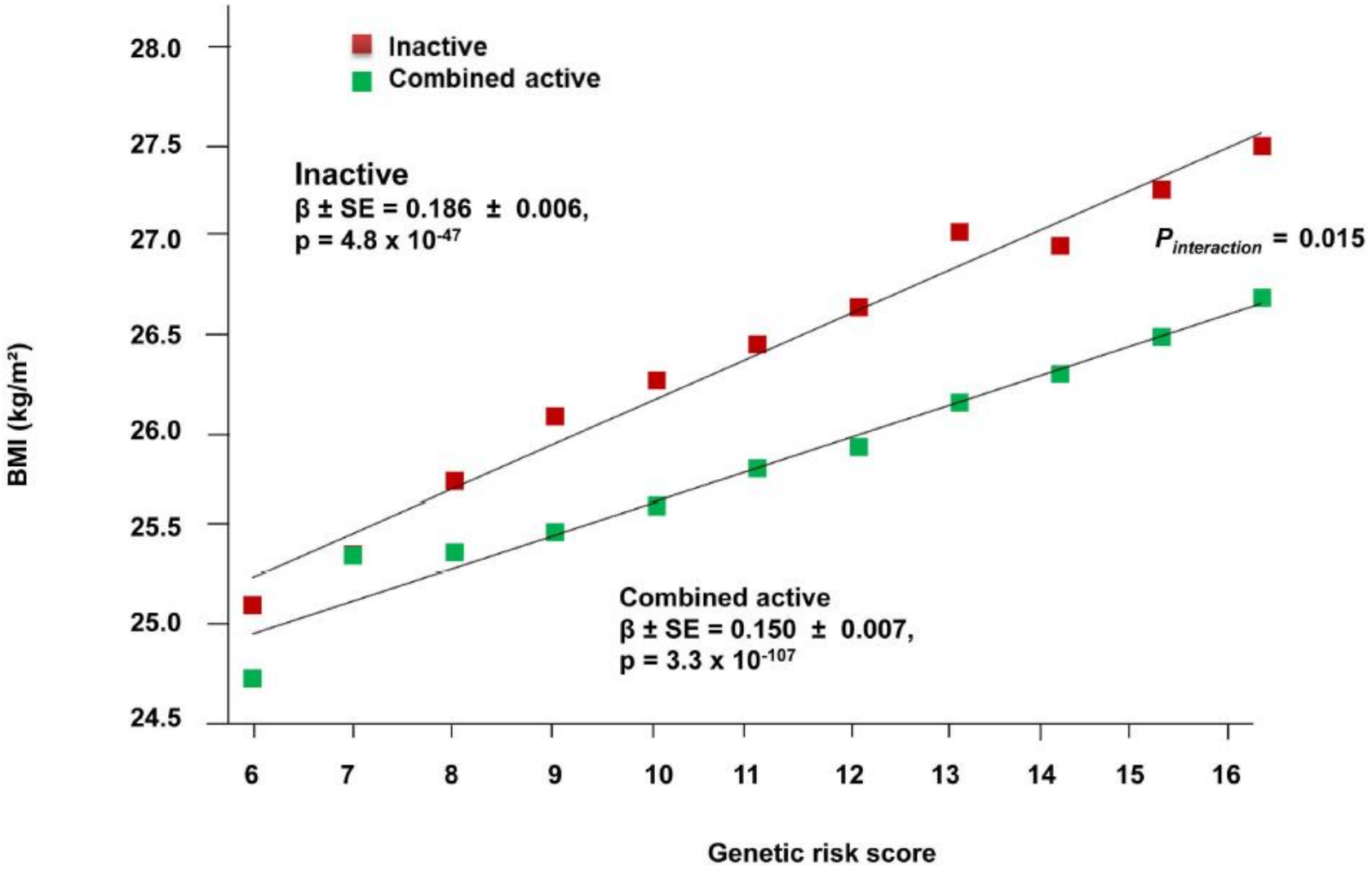


Figure 2. Association between the GRS and BMI in the inactive and 'combined active' groups (N = 111,421). Physical activity was estimated according to the Cambridge Physical Activity Index (CPAI), where the inactive group is defined as individuals with a CPAI of 1 and the 'combined active' group as individuals with a CPAI of 2–4.
doi:10.1371/journal.pgen.1003607.g002

Ahmad PLoS Genet 2013

Twin studies in analyzing gene-environment interactions

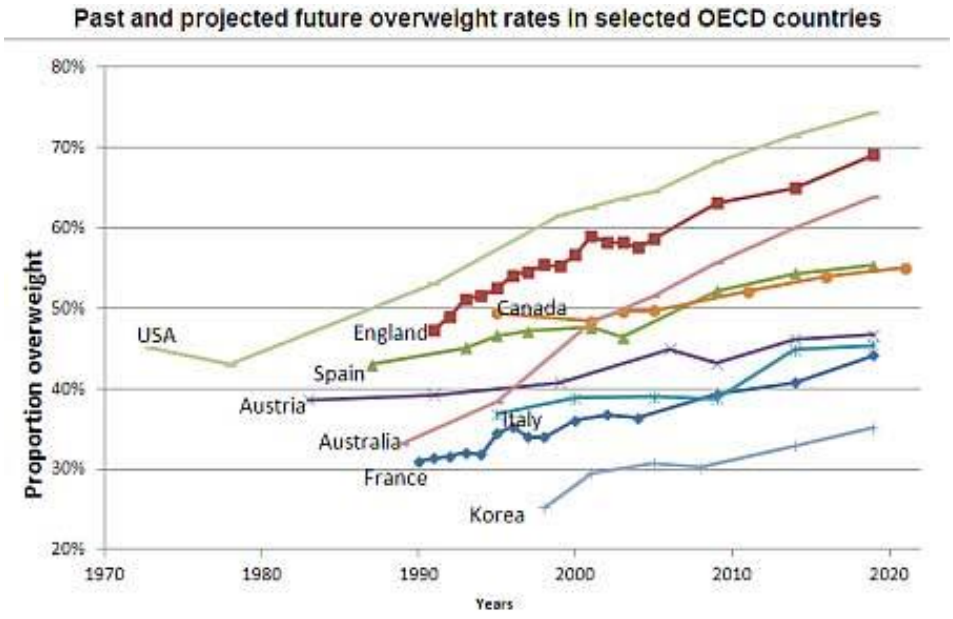
Opportunities of twin studies

- Even when it is possible to analyze how environment modifies the effect of one gene or genetic risk score on a phenotype, twin studies of G-E interaction are still useful
- Twin design allows to analyse total genetic variation whereas GRS explain only a few percent of the variation
- For many traits, GRS or strong candidate genes are not available
- Twin data is also much easier and cheaper to collect and are available for a long period of time
- It is also possible to analyze environmental part of variation

G*E interaction based on multiple group analysis

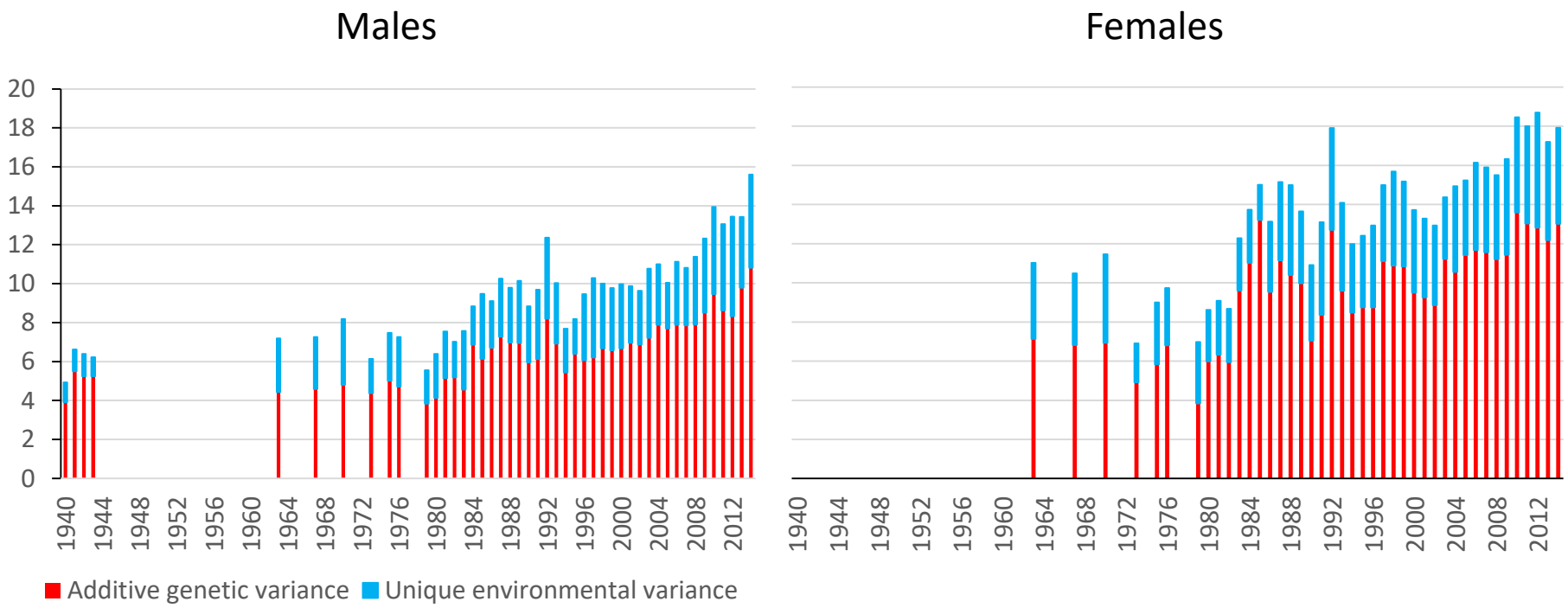
- A simple way to analyze G-E interactions is to stratify the data by the environmental exposure
  - Run genetic twin model in several groups and study differences between the variance components
- Thus, we can simply utilize multiple group comparison using univariate models
- Significant differences in genetic and/or environmental variance components across the categories indicate the existence of G-E interaction
  - Can be tested by χ^2-statistics
- Shows how simple methods can sometimes be used to answer complex research questions

Trends of overweight in the world



- Similar trends in overweight and obesity have been found all over the world
- However, also remarkable differences between countries
- Not directly associated with standard of living
- Obesity levels are highest in USA and lowest in East-Asia
- May indicate cultural factors such as traditional diets
- Consumption of meat vs. vegetables

Additive genetic and unique environmental variance of BMI by measurement year



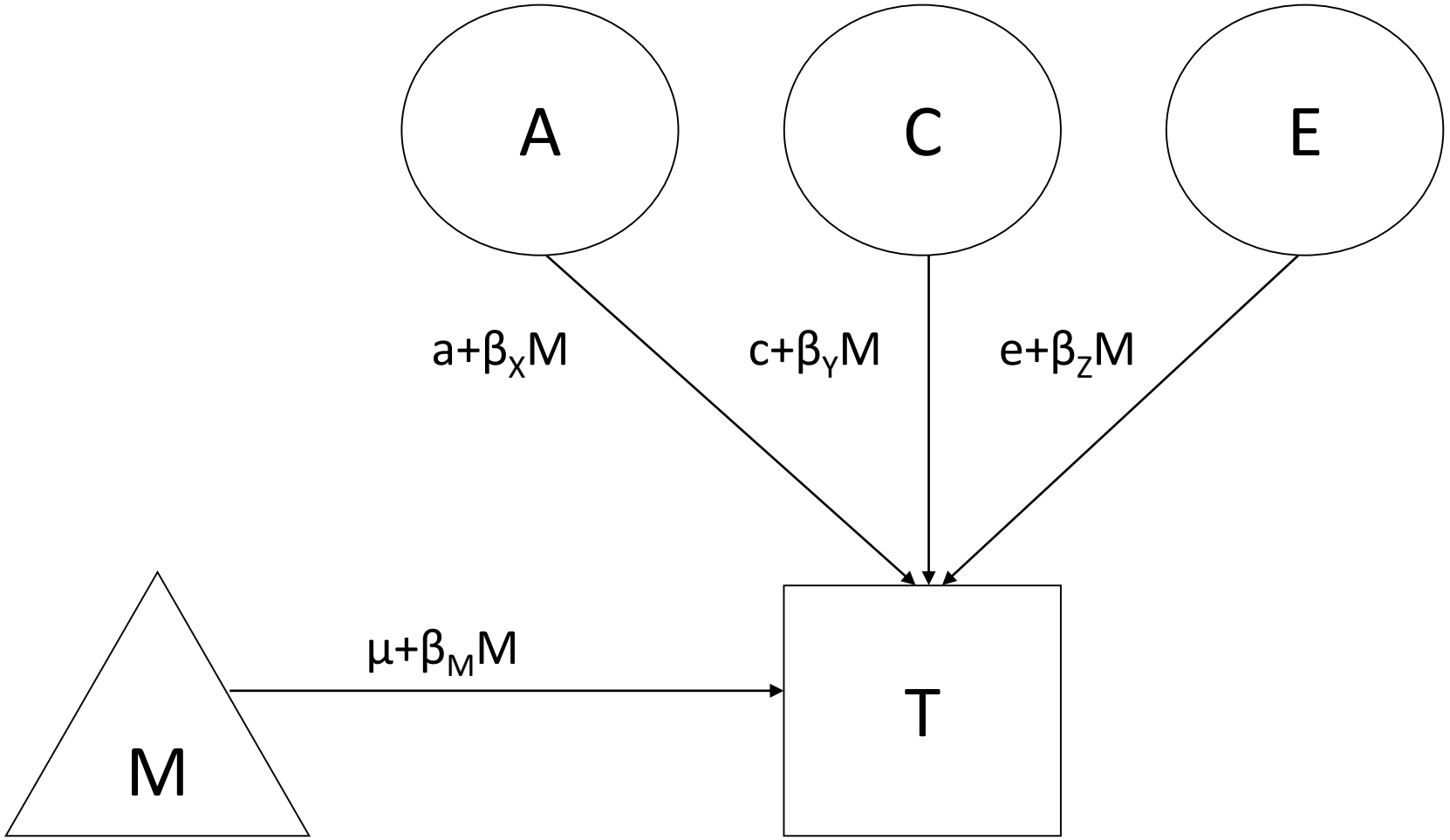
Silventoinen et al. (2017) Am J Clin Nutr

Problems in multiple group comparisons

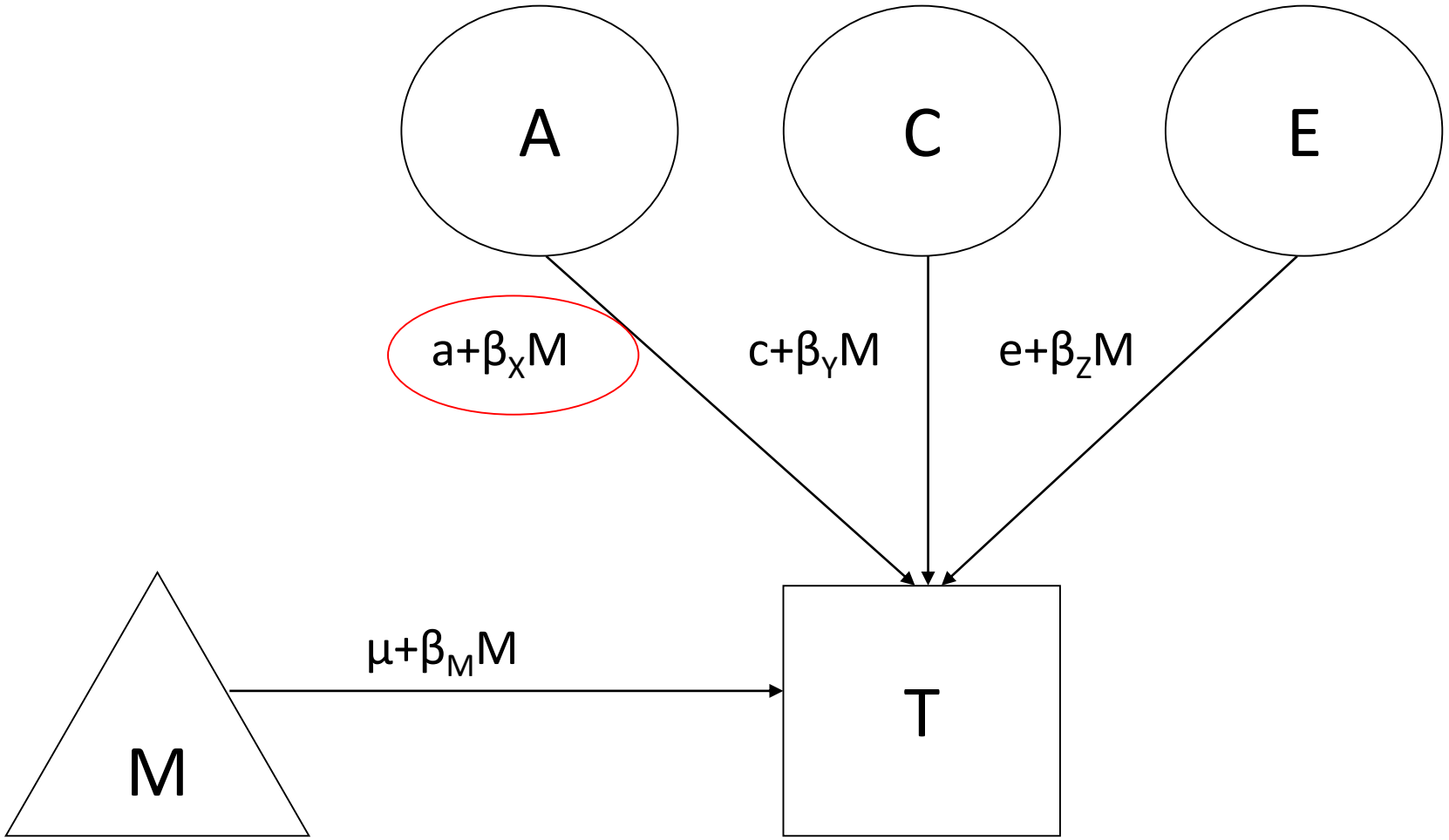
- Multiple group comparisons have limitations, which make them unsuitable to many situations
- Environmental exposure needs to be same for both co-twins
  - Such as birth cohort or place of residence
- If environmental exposure is continuous, categorizing it loses a lot of information if the associations are linear
- However if this kind of limitations are not a problem, multiple group comparison is a good alternative to more sophisticated G-E interaction models
  - Interpretation of the results is very straightforward
  - Possible non-linearity is not a problem
  - We can accept heterogeneity between the categories
  - Models are very robust whereas more complex models can be sensitive to starting values
- Especially if the modifying effect does not follow any function, this approach is a good alternative
  - However, there are also statistical methods to model this type of interaction effects

Gene-environment interaction model for twins

G-E interaction model



G-E interaction model



Matrix algebra for G-E interactions

- The equation $a+\beta_X M$ is a linear function
  - Why this can be used to analyze interactions?
- We are interested in the variance component a^2 instead of the path coefficient a
- Thus $(a+\beta_X M)^2=a^2+\mathbf{2*a*\beta_X M}+(\beta_X M)^2$
- This can be easily generalized to multivariate case using matrix algebra rules

Practical

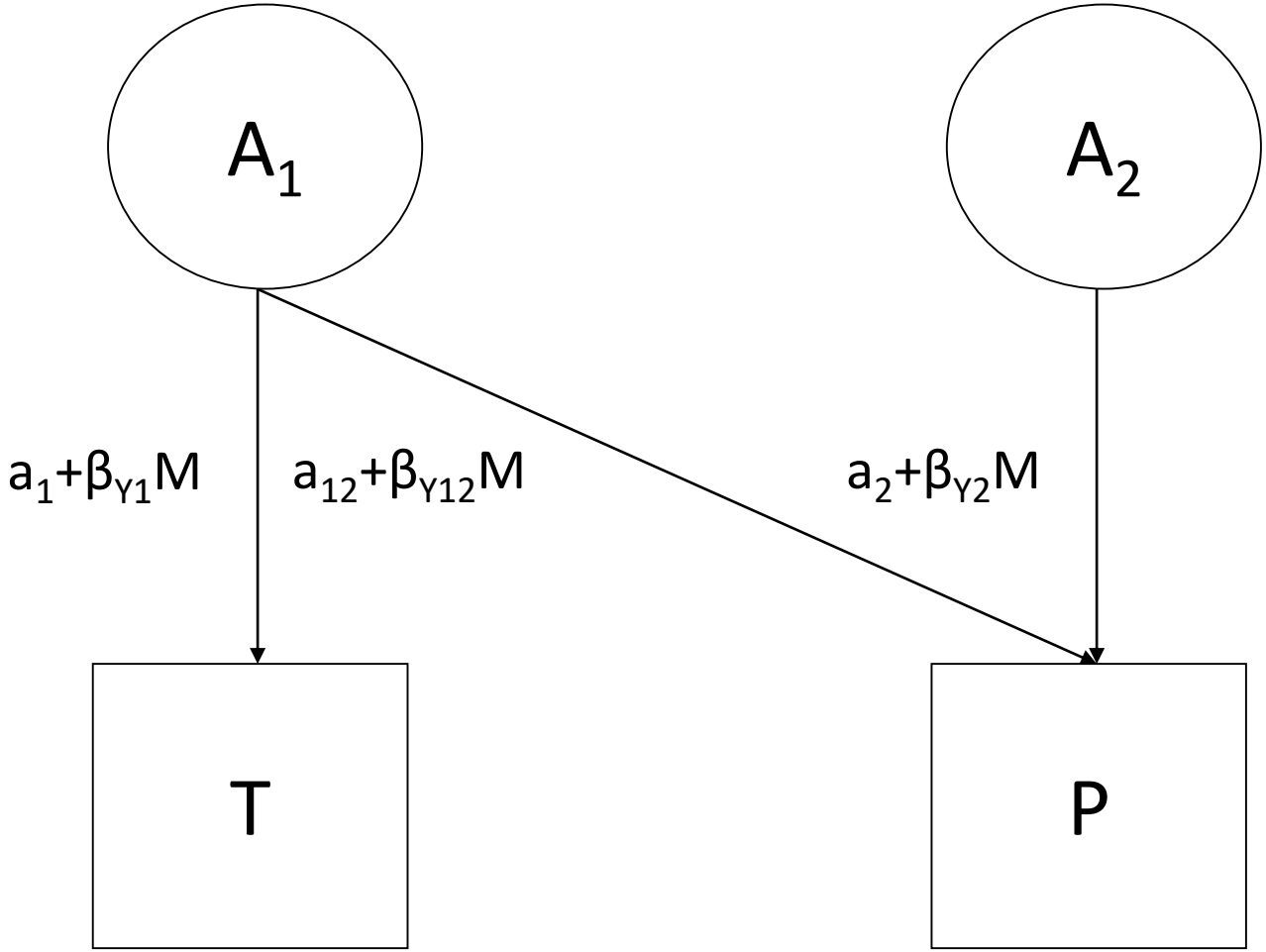
- We will analyze how age affects the variation of BMI in Finnish Twin Cohort
- Human BMI increases by age
- Is this affected by increased environmental or genetic variation?
- Script GE model.R

Starting values in GE models

- GE models can we quite sensitive to starting values
  - This is a general problem in OpenMx but it is especially difficult to GE models
- This is understable because quite similar total variance can be find by different combinations of intercept (variance in moderator value 0) and slope (change of variance as a function of moderator)
- Sometimes the model does not fit
- However, even more problematic is that the model finds a local maximum of likelihood function
- In that case, the results may change when changing the starting values
- Need to try different starting values and compare -2LL values

More complex gene-environment interaction models

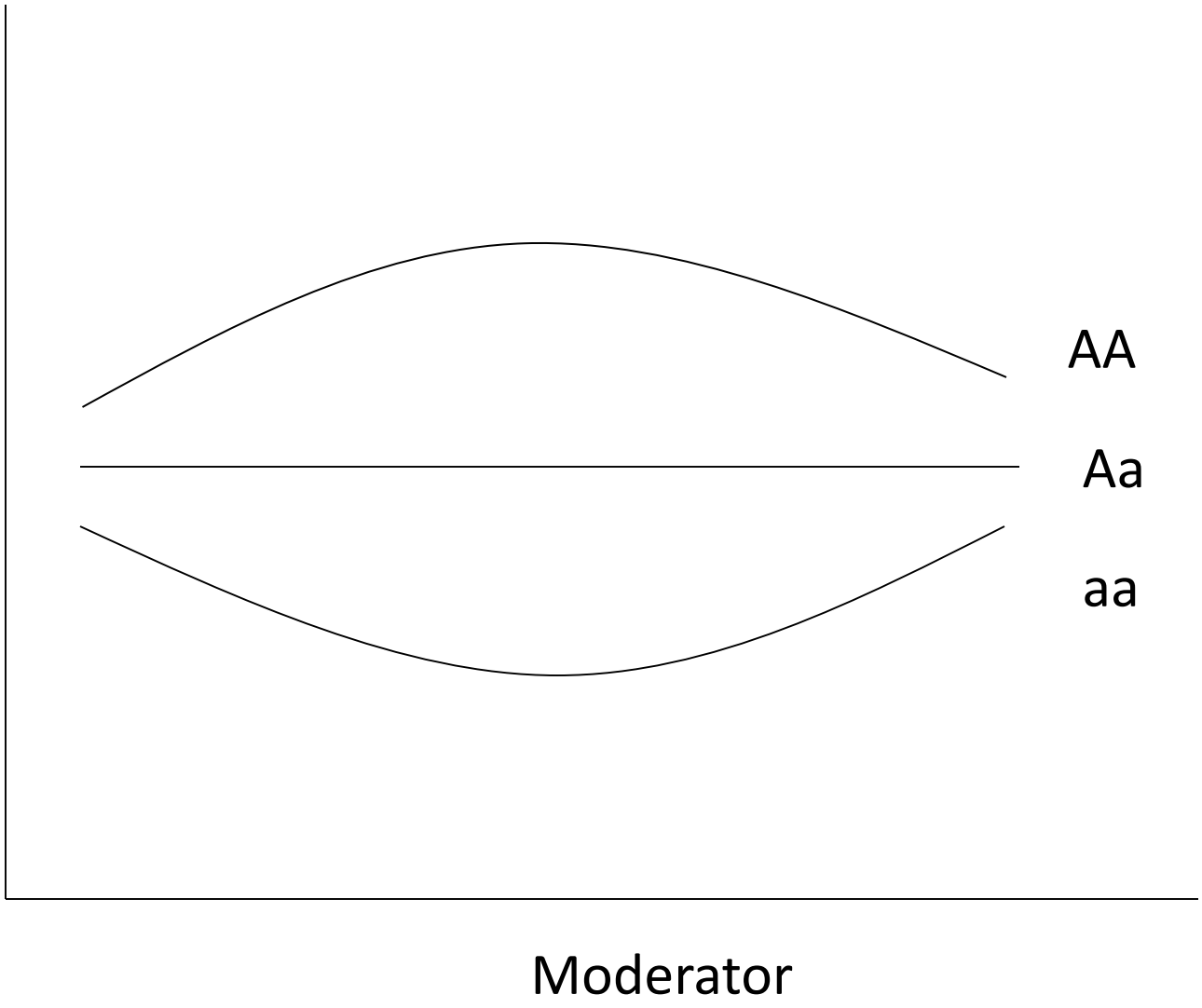
Multivariate G-E interaction model



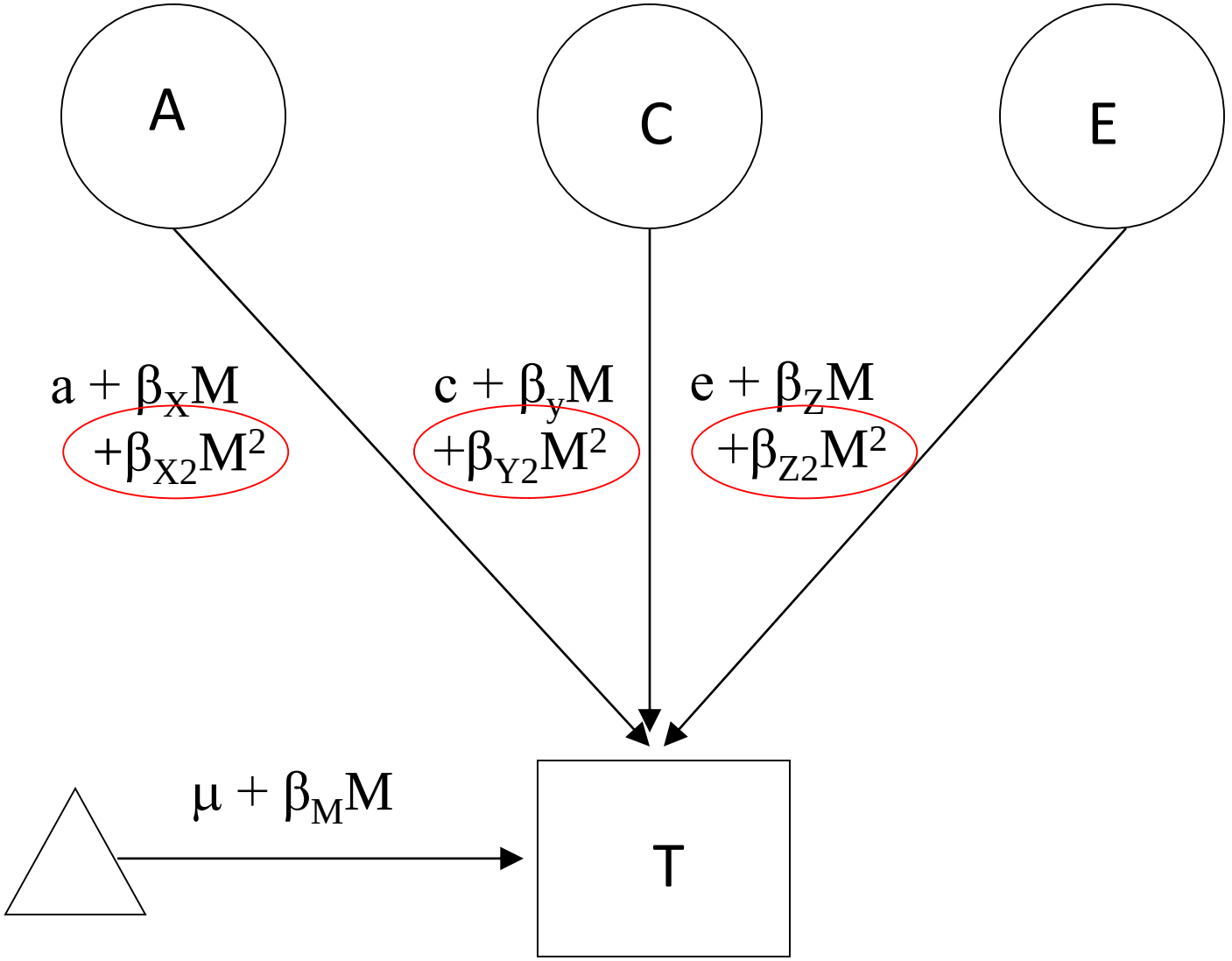
Non-linear interaction effects

- It is also possible that the effect of environmental exposure is not linear but curvilinear
- For example, genetic variation may be low both at low and high level of environmental exposure
- This can be modeled simply by including a new moderator term in the model
- Even when curvilinear effects are not difficult to model, power may be a problem
- Also the extreme ends of environmental exposures may be problematic
  - Reporting errors etc.
- Before analyzing curvilinear associations, there should be clear theoretical justification why we expect this kind of associations
- Sample size should also be large and the measurement of environment high quality

Nonlinear Moderation



Nonlinear Moderation can be modeled with the Addition of a quadratic term



Addiction
RESEARCH REPORT
doi:10.1111/j.1360-0443.2008.02375.x

Genetics of coffee consumption and its stability

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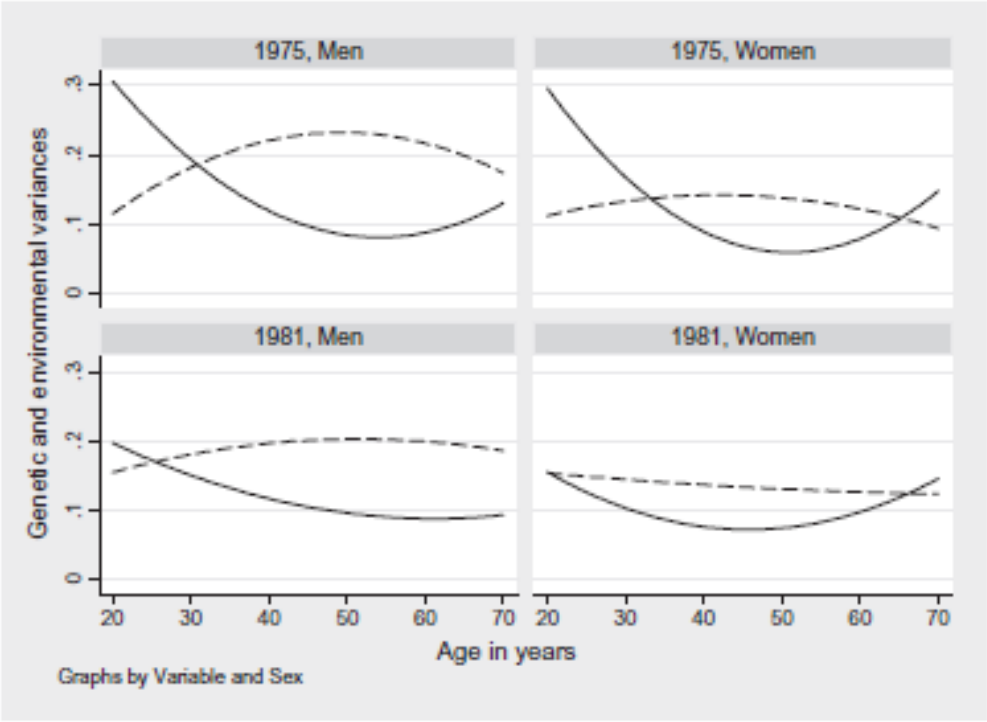

Figure 1 Changes of additive genetic (continuous line) and unique environmental (dashed line) variance with increasing age in quadratic gene–environment interaction model

Genetics of coffee consumption and Finnish culture

- Coffee consumption is highest in Finland in the world (9.9 kg/person/year)
  - This is quite a lot especially when considering that usually only adults drink coffee in Finland
- In Finland, it is very common that in work contracts it is said that employees can have two 12 minutes coffee breaks (this term is used) payed by the employer
  - Tea is also consumed but much less than coffee and traditionally it is consumed at evening
- Thus, coffee drinking is an important social event in many work places
- This may explain the lower genetic variation of coffee consumption in working age population
- Many persons who do not initially like coffee, may start to drink it at work because of social reasons
- The effect may have declined from 1971 to 1982 when tea has become a more common alternative to coffee also at daytime

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