Summary and Conclusions

The most important finding that has emerged from this study is that the familial aggregation that was observed for cardiovascular risk factors is predominantly caused by genetic influences shared by parents and their children rather than by common environmental factors shared by family members. A summary of the heritabilities of the cardiovascular risk factors that were studied in Dutch twins (14-21 years) and their parents (35-65 years) is presented in Table 1.

Table 1: Heritabilities (expressed as percentages of total variances) for cardiovascular risk factors

RSA, SBP, DBP measured during rest and mental stress conditions (reaction time (RT) and mental arithmetic (MA) task) in 160 adolescent twin pairs

	Heritability					
	Rest1	Rest2	RT1	RT2	MA1	MA2
Respiratory sinus arrthythmia	29	37	43	48	51	51
Systolic blood pressure*	52	55	61	64	62	66
Diastolic blood pressure*	57	51	59	58	64	53

Cholesterol,(Apo)lipoproteins, Lathosterol, Phytosterols, HRG measured in 160 adolescent twin pairs and their parents

	Heritability	
	Parents	Children
Total cholesterol	29	81
Triglycerides	10	65
High-density lipoprotein	35	71
Low-density lipoprotein	37	82
Apolipoprotein-A1	35	78
Apolipoprotein-A2	50	80
Apolipoprotein-B	38	81
Apolipoprotein-E	31	87
Lipoprotein(a)	98/93	98/93**
Lathosterol	29	29***
Campesterol	80	80
beta-Sitosterol	73	73
Histidine-rich glycoprotein	69	69

Sport Smoking

Sports participation (measured in 90 twin pairs and their parents) and smoking behavior (measured in 1600 twin pairs and their parents)

	Heritability	Common Environment
Sport	64	0 / 28**
Smoking	39	53

* Results from univariate analyses. Multivariate analyses also revealed contributions of shared environment for SBP in males and females and DBP in females, especially in the rest conditions.
** First estimate applies to males, second estimate to females.
*** In addition, for lathosterol common environmental influences shared by siblings accounted for 37% of the total variance.

Respiratory sinus arrthythmia, systolic and diastolic blood pressure

Respiratory sinus arrthythmia (RSA) reflects the cyclic variations in heart rate that are related to respiration and has been shown to be a sensitive index of vagal cardiac control. High RSA is regarded as an index of good health, both with respect to cardiovascular and central-nervous system functioning. We observed a large influence of mental stress tasks on RSA heritability. Under conditions of mental stress RSA heritability was twice as large as during rest. Multivariate analyses demonstrated that the amount of genetic variance in RSA was the same during rest and stress, but that environmental variance not shared between family members decreased substantially during mental stress conditions. Multivariate genetic modelling also revealed that the same genes are expressed during rest and stress conditions. Thus, individual differences in vagal tone that are genotype dependent are more accurately assessed during stress than under rest conditions.

For blood pressure similar effects of mental stress on heritabilities were seen. Univariate analyses gave no evidence for sex differences in heritabilities in any of the conditions. Multivariate analyses showed that intercorrelations between blood pressure assessed in different conditions were significantly lower in females than in males. Multivariate genetic model fitting was therefore carried out separately for males and females. For SBP and DBP in females and for SBP in males heritabilities increased and the influences of shared environment decreased during mental stress as compared to rest. For DBP in males no significant contributions of shared environment were found. The multivariate analyses indicated that the same genes and environmental influences are expressed during rest and task.

Cholesterol, lipoproteins and apolipoproteins

Marked differences between generations in phenotypic variances and heritabilities were observed for all lipid, lipoprotein and apolipoprotein parameters. The best fitting model to parent-twin data indicated that increases in phenotypic variances in the parental generation were caused by an increase in environmental variances as people grow older. The amount of genetic variance for nearly all traits was the same in adulthood as in adolescence, thereby leading to a decrease in heritabilities. However, these analyses were based on the assumption that the genes that influence variation in lipids and (apo)lipoproteins in the offspring are the same genes that are expressed in their parents. To obtain an estimate of the correlation between genetic influences expressed during adolescence and adulthood, longitudinal data from genetically informative subjects are needed. An alternative to a longitudinal study is to augment the present design with data from a sample of twins of the same age as the parents of the twins from this study. In that case, heritabilities can be estimated for each generation separately, based on the information available from adolescent and adult twins. If these heritabilities are known, the observed parent-offspring correlation can be used to estimate the correlation between genetic values in adolescence and adulthood (Stalling, Baker & Boomsma, 1989). Likewise, the stability of environmental effects across adolescence into adulthood can be estimated. Such a project is currently underway. A second possibility that can be examined if data from an older twin sample become available, is that part of the increased environmental variance consists of variance caused by genotype x environment (GxE) interaction, which in regular covariance structure models cannot be distinguished from the random environmental component. With multivariate lipid data from adolescent twins and their parents and from an older twin cohort, individual factor scores may be computed that can be used in tests of GxE interaction (Molenaar & Boomsma, 1987).

Lipoprotein(a)

Recent studies suggest that much of the risk associated with a positive family history for coronary heart disease may be attributed to variation in plasma lipoprotein(a) [Lp(a)] concentrations. For example, Hoefler et al. (1988) observed significant differences in Lp(a) levels between young offspring whose parents suffered from myocardial infarction and age matched controls. No other lipid or lipoprotein parameters differed between these two groups. Durrington et al. (1988) found that apolipoprotein(a), the essential protein component of Lp(a), could be substituted for parental history of coronary heart disease in a discriminant analysis of infarction patients and controls. In the present study heritability for plasma Lp(a) concentrations was higher than for any other trait. There were no intergenerational differences in heritability be tween parents and offspring. A large part of the genetic contributions to variation in Lp(a) concentrations probably can be attributed to the apo(a) locus at chromosome 6 which is highly polymorph. We are currently measuring apo(a) phenotypes of all subjects who participated in this study. When this information becomes available, it is then possible to exactly quantify the contribution of the apo(a) locus against the background of the contributions of other genes.

Lathosterol, campesterol and beta-sitosterol

Lathosterol, an indicator of whole-body cholesterol synthesis, was one of the few variables in this study for which a significant contribution of common environment shared by siblings living in the same family was suggested in addition to a moderate heritability. For plant sterols campesterol and beta-sitosterol genetic heritability was high and no contributions of shared environmental influences were found. Both campesterol and beta-sitosterol reflect dietary cholesterol absorption. Plant sterols are not synthesized by humans and only a small percentage of plant sterols present in the diet is absorbed. Our results strongly suggest that it is this absorption process that is under genetic control and that sharing the same diet –as was to a large extent the case for the subjects in our study- is not an important factor in determining plasma phytosterol levels.

Histidine-rich glycoprotein

Histidine-rich glycoprotein (HRG) is a non-enzymatic glycoprotein that acts as a modulator of several plasma proteins involved in coagulation and fibrinolysis, but whose physiological function has not been established yet. Elevated plasma HRG levels have been implicated in familial thrombosis and have been found in a small group of patients with myocardial infarction. It is clear from our study that the familial elevation of HRG levels has to be attributed to genetic influences shared by parents and children. Genetic influences account for a substantial part of the variance in plasma HRG concentrations and was the same in males and females and in parents and offspring. This high heritability justifies the search for quantitative trait loci which is currently underway. The search for possible non-genetic causes of elevated HRG levels should be directed towards factors outside the home environment.

Sports participation

Data on sports participation were analyzed for the first 90 families who took part in the present study. A large part of the variance in sports participation could be explained by genetic factors. There were no differences between sexes or generations in heritability. No cultural transmission from parents to offspring was seen, but in female twins there was evidence for shared environmental influences. Of course, the sample size for this analysis leaves much to be desired. However, results from a much larger sample of 1600 adolescent Dutch twin pairs and their parents point in the same direction and support our conclusions (Koopmans, Van Doornen & Boomsma, submitted).

In this larger sample it was found that 45% of the total variance was explained by genetic factors and 44% by shared environment. However, environmental factors that contributed to sibling resemblance were different in males and females. This new study did not find any cultural transmission from parents to children either.

Smoking

Smoking behavior was assessed by questionnaire in 1600 twins and their parents. For individual variation in smoking initiation, a larger contribution of shared environment than of genetic factors was found. The magnitude of the genetic and environmental influences did not differ between sexes. However, environmental effects shared by male siblings and environmental effects shared by female siblings were only moderately correlated. Twin data can be used to identify sibling interaction effects, i.e. the reciprocal influences of one twins behavior on that of the cotwin. The possibility of sibling interaction was examined for smoking status, but no interaction effects were seen. In contrast, in the male twins that participated in the present study sibling interaction was seen for type-A behavior (Sims et al., 1991). There was no evidence that smoking of parents encouraged smoking in their offspring. The resemblance between parents and offspring for smoking was significant, but rather low and could be accounted for completely by their genetic relatedness. Very remarkably, there was no difference in the associations between smoking in offspring with 'ever smoked' in parents and smoking in offspring with 'currently smoking' in parents, strengthening the conclusion that smoking in parents does not encourage smoking in children.

Blood pressure and alpha-1-antitrypsin

In the parents of twins that participated in the present study a beneficial effect of alpha-1-antitrypsin (AAT) deficiency alleles S and Z was seen on blood pressure. This effect was strongest for systolic blood pressure measured in males for whom differences between MM homozygotes and MZ and MS heterozygotes could be as much as 11 mmHg. Non-MM males not only had lower resting values, but also were less reactive with their blood pressure to mental stressors. A similar trend was observed in mothers of twins, but not in the twins themselves. This is the first finding of a beneficial effect of AAT deficiency alleles on blood pressure and it was subsequently replicated in a 10-year old Australian data set. For Australian males (on average only 9 years older than the twins participating in our study) a similar effect of AAT deficiency alleles on systolic and diastolic blood pressure was found. However, in females from the Australian study no such effects could be detected. These results suggest a complex interaction between sex and age on the effects of AAT alleles on blood pressure.

General Conclusions

The familial aggregation that is seen in this sample of Dutch families for factors associated with risk of cardiovascular heart disease is for most of these factors caused by genetic influences shared by parents and children. For some of the variables that we measured -RSA, lathosterol, the phytosterols, plasma apolipoprotein E levels, histidine-rich glycoprotein- this is the first time that their heritabilities have been estimated in a general population sample. For other variables, e.g. smoking behavior, this is the first study to assess heritability in a sample consisting of adolescent twins and their parents.

For most cardiovascular risk factors the influence of common environmental factors shared by family members was not large, despite the fact that our sample consisted entirely of parents and offspring sharing the same household.

Significant influences of shared environmental factors were observed for blood pressure, lathosterol, sports participation and smoking behavior. For lathosterol and both behavioral traits the analysis of the parent-offspring data indicated that the relevant common environmental factors were shared between siblings, but not between parents and offspring. The resemblance that was found between parents and children was accounted for completely by their genetic relatedness. Shared environmental influences on blood pressure were mainly observed for blood pressure assessed during rest conditions.

The absence of common environmental influences implies that we need to look for environmental causes of variation in cardiovascular risk factors outside the home environment. One such cause that may be important is genotype by environment (GxE) interaction. Within our LISREL-based quantitative genetic approach a new test for such GxE interactions has been developed which can be applied to multivariate phenotypes. The test does not require the actual measurement of genotype or environment and hence is especially suited to apply to human phenotypic data. Proceeding along these lines, we can also speculate about alternative sources of phenotypic variation disguised as specific environmental influences, but in reality due to nonlinear growth processes (Molenaar, 1992).

To all risk factors that we studied elaborate models were fitted that specified sex differences in the genetic architecture of these traits, but very little evidence for such sex differences was found.

Heritabilities for cardiovascular risk factors measured in adolescent twins were high, above 50% for nearly all traits that were studied. These substantial heritabilities justify the search for major genes that may influence variation in continuously distributed traits.