Summary

In this thesis, a series of studies were conducted to investigate different aspects of the genetics of eating disorders. Eating disorders are distinguished into anorexia nervosa (AN), bulimia nervosa (BN) and eating disorders not otherwise specified (EDNOS). Chronicity and mortality of patients with eating disorders are among the highest of all psychiatric illnesses. Despite substantial efforts to identify causal pathways for AN and BN, very little is known about the aetiology of eating disorders

Chapter 2 reviews the different studies that have been performed to explore the biological background of eating disorders. Family studies have shown that AN and BN are strongly familial, and that familial aetiologic factors appear to be shared by both disorders. Twin studies mainly focussed on broader phenotypes or subthreshold eating disorders. These studies consistently yielded moderate to substantial heritability estimates for both AN (ranging between 48 and 76%) and BN (ranging between 30 and 83%). However, due to the low prevalence of both disorders, and subsequently the small numbers of affected twins, the statistical power, even when using broader phenotypes, was far from adequate. Genomewide screens have demonstrated linkage peaks for AN on chromosomes 1p33-36 and 4q13, for AN including behavioral covariates on chromosomes 1q31, 2p11 and 13q13, and for BN on chromosomes 10p13, and 14q22-23. Many genetic association studies have been conducted in eating disorders, in which genetic variation within a candidate gene is compared between cases and controls. Nearly all of these studies did not lead to any definite conclusion. Typical of the association studies in this field is the excess of small, discrepant studies.

In chapter 3 we evaluated whether the disordered eating behavior (DEB)-scale was comparable between men and women. We described five different steps of a multi-group discrete factor analysis accumulating into a model of complete measurement invariance, which was applied in a sample of 1195 adolescent men and 1507 adolescent women from the Netherlands Twin Registry (NTR). DEB was the sum score of four items on clinical features from different eating disorders: dieting, fear of weight gain, importance of body weight or shape on self-evaluation and binge eating. For DEB, the model of full measurement invariance with respect to sex (model 5), did not fit the data well. If this model had fitted, the probability of a certain response on a given item would have been the same for all participants with the same value on the underlying trait (DEB) regardless of the sex of the participant. However, this was not the case. The underlying common factor might not be the only source of difference between the sexes with respect to the four items. The sum score based on the four eating disorder items therefore cannot be taken to represent exactly the same underlying trait in men and women. This means that sex differences in this sum score might be due to measurement bias instead of a true difference in the underlying trait.

In chapter 4 we reported the results of a bivariate twin study on DEB and body mass index (BMI) in 474 monozygotic twin pairs (194 male and 280 female pairs), 310 dizygotic twin pairs (140 male and 170 female pairs), and 45 incomplete twin pairs (22 men and 23 women) from the NTR. The sibling group was comprised of 69 brothers and 115 sisters. Because the DEB items were not measurement invariant with respect to sex (chapter 3), the genetic analyses were performed separately in men and women. Twin-, cross-twin, and twin-sibling correlations indicated that a large part of the variance in both DEB and BMI was explained by genetic factors, and that genetic components were underlying the overlap between DEB and BMI in women. The bivariate analysis showed that DEB is a highly heritable trait in women (a^2=0.65) and moderately heritable in men (a^2=0.39), whereas BMI is highly heritable in both women (a^2=0.80) and men (a^2=0.76). The remaining variance in both traits was explained by unique environmental factors. In addition, additive genetic factors were responsible for the total overlap between the two characteristics, yielding a genetic correlation of 0.43 in women and 0.51 in men. Despite the overlap between BMI and DEB, the majority of the genetic influences on DEB were due to genetic effects that are independent of BMI in women as well as men.

Based on the overview of genetic studies presented in chapter 2 and the update given in chapter 1, it is clear that the serotonin pathway has mostly been indicated as relevant in the development of eating disorders, because of its involvement in a broad range of biological, physiological and behavioral functions, for example body weight regulation, eating behavior, perfectionism, impulsivity and obsessionality. But the involvement of many other candidate genes has also been studied in eating disorders. So far the only association with a ‘hypothesis based’ candidate gene that has been

observed in at least two large association studies was between brain-derived neurotrophic factor and AN. From a 'hypothesis free' approach the associations with two candidate genes have been observed in at least two large studies, namely serotonin receptor 1D and opioid receptor delta 1.

In chapter 5, we evaluated the association of 25 SNPs from four candidate genes serotonin receptor 1D (HTR1D), stathmin (STMN1), brain-derived neurotrophic factor (BDNF) and tryptophan hydroxylase 2 (TPH2), with both AN and eating disorders characterized by self-induced vomiting (SV). First, we performed genetic association analyses in cases from the GenED study (182 AN cases and 149 SV cases) and random controls from the NTR (N=607). A nominal significant association (p<0.05) was observed for TPH2 rs1473473 in AN as well as SV. This SNP was subsequently tested for replication in a meta-analysis with two additional independent eating disorder case-control samples from Germany and the Netherlands together providing 887 AN cases, 306 SV cases and 1914 controls. For the minor C-allele (frequency 0.16) of TPH2 SNP rs1473473 a significant association was observed in the meta-analyses with both AN and SV. We observed an OR of 1.25 (95% CI 1.06-1.47, p<0.009) for AN, and an OR of 1.34 (95% CI 1.06-1.69, p=0.013) for SV. The OR for the combined group of AN and/or SV cases (n=1073) was 1.24 (95% CI 1.06-1.44, p<0.006). Based on the genotype frequencies of the TPH2 SNP rs1473473 we expected a dominant effect to be underlying the association. Therefore, we evaluated the association with this SNP in the combined case-group under a dominant genotypic model. Homo- and/or heterozygous carriers of the minor allele of rs1473473 had a higher risk of either AN or SV (OR=1.38, 95% CI 1.16-1.64, p<0.0003). The TPH2 gene encodes the main rate-determining enzyme in the synthesis of serotonin in the brain (Zill et al., 2007). Serotonin is involved in satiety, anxious and obsessional behavior, mood, and impulse control, features all linked to eating disorders (Kaye, 2008; Lucki, 1998).

Chapter 6 explored the hypothesis that genetic variation in the TPH2 gene (associated to a higher risk for AN and/or SV in chapter 5), explains the overlap between eating disorders, perfectionism and impulsivity by performing three analyses. In the extensive phenotypic analyses, we confirmed earlier observations that participants with AN and/or SV score different from healthy controls on perfectionism and impulsivity as measured by the Multidimensional Perfectionism Scale and Dickman Impulsivity Inventory. To study the involvement of four TPH2 SNPs in perfectionism and impulsivity in the absence of disease, genetic analyses were performed in a random twin-based control group (N=512). We observed an association with the Youth Self Report item on impulsivity for two SNPs. The minor allele of rs1473473 (OR =1.49, 95% CI 1.02-2.17, p=0.04) and rs1007023 (OR=1.60, 95% CI 1.08-2.36, p=0.02) were more frequent in impulsive controls. Next, we tested whether these two SNPs were also associated to impulsivity (as measured by the Dickman Impulsivity Inventory) in an eating disorder case group (N=267). An association was observed for both rs1007023 (OR=1.79, 95% CI 1.01-3.17, p=0.05) and rs1473473 (OR=1.83, 95% CI 1.08-3.08, p=0.02). Genetic variation at the TPH2 gene thus appeared to affect impulsivity which in turn might predispose to the AN and/or SV phenotype.