Background: The familial accumulation of peptic ulcer disease observed in several studies may be attributable to genetic effects, aggregation of environmental exposure (shared environment), or both. The intrafamilial spread of Helicobacter pylori infection has raised the question whether shared environment could explain the familial aggregation of peptic ulcer disease rather than genetic similarity of family members.

Objective: To examine the contribution of genetic and environmental factors to the pathogenesis of peptic ulcer disease in a nationwide population-based cohort of adult twins.

Methods: The Finnish Twin Cohort consists of all same-sexed twin pairs born before 1958 with both twins alive in 1975. The total number of twin pairs is 13,888, of whom 4,307 are monozygotic (MZ) and 9,581 are dizygotic (DZ) twins. Questionnaire surveys of twins were carried out in 1975, 1981, and 1990, including medical and psychosocial questions. One question asked whether a physician had ever made a diagnosis of gastric or duodenal ulcer. In addition, hospital discharge data from 1972 to 1991 were linked with the twin cohort to obtain those twin individuals who had been treated for gastric or duodenal ulcer. The prevalence of and concordance for disease were examined in MZ and DZ twins. Model-fitting analysis was used to specify the relative roles of genetic and environmental factors. The contribution of lifestyle factors and stress was examined prospectively in an incidence study and by comparison of discordant pairs.

Results: The prevalence of peptic ulcer disease was 6.2% in men and 2.8% in women in 1975. There were 63 MZ and 86 DZ pairs concordant for peptic ulcer disease. Concordance for disease was significantly higher in MZ than in DZ twin pairs; the probandwise concordance rate was 23.6% (95% confidence interval [CI], 20.9%-26.3%) in MZ twins and 14.8% (95% CI, 13.3%-16.3%) in DZ twins. In the model-fitting analysis, a model with both additive genetic and unshared environmental effects had the best goodness-of-fit. Thirty-nine percent (95% CI, 32%-47%) of the liability to peptic ulcer disease was explained by genetic factors and 61% (95% CI, 53%-68%) by individual environmental factors. In the incidence study (logistic regression analysis of the entire cohort initially free of peptic ulcer disease, with subjects diagnosed as having peptic ulcer after 1975 as cases), current smoking (relative risk, 2.2; 95% CI, 1.5-3.2) and high stress levels (relative risk, 3.2; 95% CI, 1.4-7.6) in men and regular use of analgesics (relative risk, 3.3; 95% CI, 1.3-8.1) in women predicted peptic ulcer disease during the follow-up from 1976 to 1991. In the analysis of discordant pairs, smoking in men and regular use of analgesics in both sexes were predictors of peptic ulcer disease.

Conclusions: The questionnaire and hospital usage data on peptic ulcer disease in the population-based twin cohort suggest that the familial aggregation of the disease is modest, and attributable almost solely to genetic factors. Environmental effects not shared by family members were significant predictors of disease, and they were attributable to smoking and stress in men and the use of analgesics in women. The minor effects of shared environment to disease liability do not support the concept that the clustering of risk factors, such as H pylori infection, would explain the familial accumulation of peptic ulcer disease.
MATERIALS AND METHODS

THE FINNISH TWIN COHORT

The Finnish Twin Cohort was compiled from the Central Population Registry of Finland using selection procedures described in detail elsewhere. In brief, the Central Population Registry of Finland is a computerized database of personal information on all Finnish citizens from 1967 onward. All sets of individuals with the same birth date, the same sex, the same surname at birth, and the same local community of birth were identified. This yielded all the pairs (N=17 357) of same-sex adult twins born in Finland before 1958 with both twins alive in 1967, as well as a small number of subjects who satisfied these criteria but who were not biological twins. A baseline questionnaire, administered in August through October 1975, asked whether the subjects were twins and included questions for zygosity classification (see below). The overall response rate was 89%. From local parish records, further inquiries were made about the parents of all nonresponders and individuals with conflicting responses to the item on twinship to clarify twinship.

The questions used to assign the zygosity of twins were similar to those used in questionnaires for other large twin samples. The validity of zygosity questions was confirmed by blood typing a subsample of 104 twin pairs living in the Helsinki area. About 93% of all responding pairs were classified as MZ or DZ. Classified pairs had a 1.7% probability of misclassification. The algorithm for classifying zygosity left 7% of respondent pairs unclassified because of conflicting responses to the items. A total of 2489 pairs were left unclassified by zygosity. These also consisted of pairs with an unknown address or with nonresponse to the 1975 questionnaire. A total of 13 888 pairs (4307 MZ and 9581 DZ) were 18 years or older at baseline were identified.

QUESTIONNAIRE SURVEYS

The questionnaire surveys carried out in 1975, 1981, and 1990 contained 97 to 103 multiple-choice demographic, medical, and psychosocial questions. In each survey, twins were asked whether a physician had ever made a diagnosis of gastric or duodenal ulcer (yes or no). Smoking (none, occasionally, former smoker, or current smoking), alcohol consumption (reported use of beer, wine, and hard liquors was converted to alcohol grams and classified as: abstainer, 1-399 g/mo, 400-899 g/mo, or ≥900 g/mo), and use of analgesic drugs and antacids (none, <10, 10-59, 60-180, or >180 days yearly) were also determined. Experienced stress was measured in the 1975 questionnaire, which included 4 items of self-report of stress of daily activities presented as 4-point scales. The items of stress of daily activities were the following: (1) In general I am unusually tense and nervous; (2) there is great deal of stress connected with my daily activities; (3) at the end of day I am completely exhausted mentally and physically; and (4) my daily activities are extremely trying and stressful. There were 4 alternatives to answer: the statement describes me “very well,” “well,” “not very well,” or “not at all.” The sum scores were divided into 5 categories (none, low, some, moderate, or high). Correlation coefficients of scale items and total score distributions have been described. Stress of daily activities score has been found to predict morbidity from mental disorders in a 6-year follow-up among 31 116 Finnish adults.

HOSPITAL DISCHARGE DATA

Hospital discharge data were also used to identify twins with peptic ulcer disease. The National Agency for Welfare and Health has kept a national registry of hospital discharges since 1969. This registry covers all discharges of inpatients from all hospitals in Finland. The discharge diagnoses have been assigned by those physicians who treated the patient using the International Classification of Diseases, Ninth Revision (ICD-9). Up to 4 different diagnoses per patient could be listed at each discharge. Data from 1972 to 1991 were linked with the Twin Cohort, using the unique social security identification number assigned to each Finnish citizen, to obtain the twin individuals who had gastric or duodenal ulcer disease as a discharge diagnosis (ICD-9 codes 531-534 or their equivalents in ICD-8). By combining the questionnaire and hospital usage data, a total of 1692 twin individuals with peptic ulcer disease were identified.

DATA ANALYSIS AND STATISTICAL METHODS

Prevalence and Incidence Analysis

The prevalence of peptic ulcer disease at baseline was calculated for all individuals (twins and nontwins) who responded

Continued on next page
to the 1975 questionnaire. For the analysis of predictors of peptic ulcer disease, the cohort of individuals initially free of ulcer disease was defined as those subjects who replied also to both of the follow-up questionnaires and who at baseline reported that they did not have a history of or hospitalization for peptic ulcer disease and they did not use antacids. Incident cases of disease were those individuals who reported a physician-diagnosed peptic ulcer disease in 1981 or 1990, or who had been hospitalized for peptic ulcer in 1976 or later. Unconditional logistic regression analysis was used to estimate the odds ratios of disease by age (5 groups), smoking status (4 categories), analgesic use (5 categories), use of alcohol (4 categories), and stress of daily activities score (3 categories).

Pairwise Comparisons

Concordance.—Twin similarity for peptic ulcer disease can be summarized using estimates of concordance. Concordance can be assessed using 2 concordance rates (termed pairwise and probandwise), each calculated separately for MZ and DZ pairs. Pairwise concordance rate gives the proportion of affected pairs that are concordant and they are descriptive statistics. The probandwise concordance rate is the proportion of all probands (primarily ascertainment affected individuals) that belong to concordant pairs. This gives information on the recurrence risk of disease (corresponding to cumulative risk) associated with the degree of relationship of the pair, and this can then be compared with the risk of disease in the population at large, and with different types of relatives. The 95% confidence intervals (CIs) for concordance and discordance of peptic ulcer disease were computed. The age-adjusted relative risks (RRs) in MZ and DZ twins when 1 twin had peptic ulcer disease, compared with the population risk, were also calculated.

Model Fitting.—For the disease, which has both a genetic liability and multiple known environmental causes, the multifactorial model was considered the most appropriate to estimate the contribution of genetic factors to the underlying liability of the disease. The model assumes that there is normally distributed liability to disease, and when the threshold of liability is reached, disease becomes manifest. Both genes and environmental factors are assumed to contribute to the liability and they result from the joint effects of many genes with small effects and a multitude of environmental effects. These assumptions were considered reasonable for this analysis as most MZ pairs were discordant for disease, and there are several known environmental agents increasing risk of disease. The proportion of individuals exceeding the threshold in the population is equivalent to the population risk.

Threshold models with genetic sources of variation, ie, additive and dominance (nonadditive effects of alleles at a given locus summed over all relevant loci); and environmental sources of variation, ie, shared (family influences common to both twins) environmental or environmental sources of variation unique to the individual (ie, not shared with twin) in the underlying liability were estimated. These models can be fitted to the 2x2 contingency tables (no disease or disease in the first twin vs no disease or disease in the second twin). Both for men and women the contingency tables are set out separately for MZ and DZ pairs. These models were estimated using the Mx software as programmed for twin analyses. These models as such do not permit gene-environment analysis.

Goodness-of-fit statistics were used to assess to what degree the model specified by the investigators adequately corresponds to the data; a small goodness-of-fit square value and high P value indicates good correspondence between model and data. Alternative models that specify different components of variance can be compared by assessing the change in χ² relative to changes in the df between models.

Discordant Analysis.—Because the subjects in this study were twins, pairs discordant for incident peptic ulcer disease were identified to examine whether the risk factors of individuals with peptic ulcer disease differ from the risk factor distribution among their age-matched siblings (either MZ and DZ twins) without peptic ulcer disease. These twins represent individuals who have generally shared the same childhood environment as the exposed subject, and share part of or all their genes in descent in common. An estimate of the RR comes from the ratio of the number of pairs in which the exposed twin had peptic ulcer disease, but the unexposed twin had not, to the number of pairs in which the opposite has occurred; a multivariate extension is conditional regression analysis. The significance of a variable in the analysis was assessed by a likelihood ratio test.

dance in MZ twins should be equal to that in DZ twins. Twin studies have supported the concept that a large part of the familial aggregation is attributable to genetic factors. The concordance in MZ twins has varied between 14.0% and 80.0% and that of DZ twins between 0% and 35.7% (95% confidence intervals (CIs) for concordance and discordance of peptic ulcer disease were computed. The age-adjusted relative risks (RRs) in MZ and DZ twins when 1 twin had peptic ulcer disease, compared with the population risk, were also calculated.

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RESULTS

PREVALENCE

The number of individuals with peptic ulcer disease is shown in Table 1. All individuals who responded to the questionnaire in 1975 were included. The overall prevalence of peptic ulcer disease was 6.2% in men and 2.8% in women. The prevalence increased with age, being 14.4% in men and 6.7% in women older than 65 years. Of twin individuals who responded to all 3 questionnaires, 784 (7.3%) of 10 807 reported peptic ulcer and 98 (0.9%) of them also had a discharge diagnosis of peptic ulcer disease. Seventeen subjects did not report peptic ulcer disease, although they had a discharge diagnosis.
INCIDENCE AND EFFECT OF RISK FACTORS

Of twin individuals who at baseline had no history of peptic ulcer disease, no hospitalization before 1976, nor any use of antacids, 197 men (4.7%) and 171 women (3.2%) reported peptic ulcer disease during the 15-year follow-up. Common risk factors of peptic ulcer disease were compared in these cases and in those who remained free of peptic ulcer disease. In the logistic regression analysis (including age group, smoking, use of analgesics, use of alcohol, and stress of daily activities score), current smoking in men and long-term use of analgesics in women and high stress score of daily activities in both sexes predicted peptic ulcer disease (Table 2).

PAIRWISE COMPARISONS

Concordance

Pairs in which both twins responded to the questionnaire in 1975, 1981, or 1990 are included in the analyses. Cases are subjects who reported a history of peptic ulcer disease in a questionnaire or who had been hospitalized. The prevalences did not differ between MZ and DZ twin individuals. The pairwise and probandwise concordance rates are also shown in Table 3. There were 63 MZ and 86 DZ pairs concordant for peptic ulcer disease.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Odds Ratio (95% Confidence Intervals)</th>
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<tbody>
<tr>
<td>Age group in 1975, y</td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>36.8, 1.0</td>
</tr>
<tr>
<td>25-29</td>
<td>23.4, 0.84 (0.50-1.42)</td>
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<tr>
<td>30-34</td>
<td>16.4, 0.72 (0.40-1.33)</td>
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<tr>
<td>35-39</td>
<td>12.2, 0.69 (0.35-1.37)</td>
</tr>
<tr>
<td>40-45</td>
<td>11.2, 1.34 (0.75-2.39)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>37.9, 1.0</td>
</tr>
<tr>
<td>Occasionally</td>
<td>4.3, 0.35 (0.00-2.26)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>19.6, 1.09 (0.58-2.05)</td>
</tr>
<tr>
<td>Current</td>
<td>38.2, 2.19 (1.36-3.55)</td>
</tr>
<tr>
<td>Stress of daily activities score</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19.2, 2.23 (1.10-4.51)</td>
</tr>
<tr>
<td>Low</td>
<td>3.1, 3.21 (1.04-9.89)</td>
</tr>
</tbody>
</table>

*Subjects initially reporting no history of peptic ulcer disease, no prior hospitalization for ulcers, and no use of antacids at baseline. Relative risks are based on odds ratios from logistic regression analysis adjusted for smoking, age, use of analgesics and alcohol, and stress of daily activities score. P values from likelihood ratio test comparing models with and without the variable in the model.
The purpose of this nationwide twin study was to examine the roles of genetic and environmental factors in the
origin of peptic ulcer disease. The higher concordance rate for peptic ulcer disease among MZ pairs compared with DZ pairs and the population risk indicates a genetic liability. In the model-fitting analysis, the model with both additive genetic and unshared (unique) environmental effects had the best goodness-of-fit value. Approximately 40% of the variability of susceptibility to peptic ulcer disease is attributable to genetic factors, while the remainder is attributable to individual environmental effects or measurement error. Despite the higher prevalence of peptic ulcer disease in men than in women, the relative roles of genetic and environmental factors in disease liability seem to be equal.

In the Swedish twin study, the same rearing environment contributed to familial similarity for acquired H pylori infection, but the extent of shared environmental effect was only 20%, while the extent of the genetic effect was 66%. In our study the model with shared environmental effects fit the data poorly, suggesting that the intrafamilial transmission of H pylori infection cannot explain the familial aggregation of peptic ulcer disease without genetic traits. The shared environmental effects measured come mostly, but not necessarily, from the childhood family. In our study, there were also 240 twin pairs who had lived together even in adulthood, and the comparison of these pairs with the pairs who did not live together showed no difference. This also confirms the finding that the shared environmental effect did not exist. The reason why the shared environmental effect was not seen in peptic ulcer disease, although it was present in acquisition of H pylori infection, may be attributable to the multifactorial origin of peptic ulcer disease; H pylori infection is just one major risk factor for the disease, and the majority of people with H pylori infection do not develop peptic ulcer disease in their lifetime. Another explanation would be that H pylori is so prevalent in the population studied that its effect on variation in risk of peptic ulcer disease cannot be detected. Our study does not contradict the theory that the inheritance of peptic ulcer disease could be mediated by the genetic susceptibility to acquisition of H pylori infection.

The direct influence of H pylori infection on disease liability was not possible to examine in this study. On the other hand, detailed data on other environmental risk factors such as smoking, use of alcohol, use of analgesics, and mental stress were available. The incidence study and the analysis of discordant twin pairs showed that smoking and mental stress in men and the use of analgesics in women predicted peptic ulcer disease. The growing use of nonsteroidal anti-inflammatory drugs has risen as the major cause of peptic ulcer disease aside from H pylori infection. On the one hand, with the exception of acute stress ulcer found most often in children and critically ill patients, findings have been conflicting regarding the role of stress in the development of peptic ulcer disease. In a cohort study by Anda et al., self-perceived stress predicted peptic ulcer disease during the 13-year follow-up (RR, 1.8). On the other hand, none of the psychological indicators were associated with an increased risk of peptic ulcer disease in a large Norwegian population-based survey.

In the discordant analysis of the Danish twin study, mentally distressing family and occupational conditions were associated with an increased risk of peptic ulcer disease, but the influence of smoking and alcohol was not studied.

Selection bias in twin studies can influence estimated heritabilities for chronic diseases and cause overestimation of the concordance rates in geographically or otherwise restricted samples. In our study, the sample was based on an unselected nationwide twin population. Since MZ twins are more similar than DZ twins with respect to smoking, food habits, physical activity, and many other behavioral characteristics, the heritability can also be overestimated. Our findings are consistent with previous twin studies regarding the genetic contribution in peptic ulcer disease. In our study, moreover, the detailed data from the 1975 survey also made it possible to specify the effects of genetic and several environmental factors.

The information on peptic ulcer disease was based on self-reports by subjects susceptible to errors because of problems in recall or validity of the questionnaire. Diagnosis was not ascertained by review of medical records. Of the subjects who responded to all 3 questionnaires, 17 had a discharge diagnosis of peptic ulcer disease without reporting it. While there are no endoscopically controlled studies on the validity of the peptic ulcer disease data collected by the questionnaire, the comparison of questionnaire and medical record data is available. In a Danish cohort study, the questionnaire data controlled by the reviewing of medical records revealed 4.3% false-positive and 3.1% false-negative statements of ulcer occurrence. In Finland, peptic ulcer disease represents a well-defined entity, and it is generally distinguishable from dyspepsia. We suggest that this simple ques-
tion offers considerably valid information without a meaningful possibility for misunderstanding. In fact, the prevalence of peptic ulcer disease in our study was comparable to a Finnish population study, in which the prevalence of endoscopically verified peptic ulcer disease or ulcer scar was 5.9%. In the study by Ando et al., the lifetime ulcer prevalence was also consistent with the prevalence in our study, being 7.7% in men and 3.6% in women (6.2% and 2.8% in our study), with a men-to-women ratio of 2:1.1 (2.2:1 in our study). Also the age distribution of ulcer prevalence was similar to that in the present study. The similar prevalence figures also suggest that our questionnaire presumably provided a reasonably valid estimation of the prevalence of peptic ulcer disease.

A limitation of our study was that gastric and duodenal ulcer disease were not asked about separately in the questionnaire. Different pathogenetic mechanisms are probably involved in the susceptibility of these 2 entities. The contribution of a genetic transmission and H pylori infection has been proposed especially in duodenal ulcer disease, while the use of nonsteroidal anti-inflammatory agents has been considered a major risk factor in gastric ulcer disease.

In conclusion, the questionnaire and hospital usage data on peptic ulcer disease in the population-based twin cohort suggest that the familial aggregation of the disease is modest, and attributable almost solely to genetic factors. Environmental effects were not attributable to factors shared by family members, and they were related to smoking and stress in men and the use of analgesics in women.

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