Lifestyle related risk factors in the aetiology of gastro-oesophageal reflux

M Nilsson, R Johnsen, W Ye, K Hveem, J Lagergren

Gastro-oesophageal reflux disease (GORD) is a considerable health problem in Western societies. The prevalence of reflux symptoms is high, and these symptoms strongly decrease the quality of life of those affected. Treatment of reflux, both pharmacological and surgical, is very costly. Furthermore, symptomatic GORD is the strongest known risk factor for adenocarcinoma of the oesophagus.

True knowledge about the aetiology of GORD is limited because of a scarcity of valid, population based data of sufficient statistical power. The need to cover this gap of knowledge has recently been emphasised.

A population based study comparing reflux symptoms in monozygotic and dizygotic twins showed that genetic factors might contribute by 31% to the aetiology of symptomatic GORD. Although genetic factors are involved, reflux is likely to be caused mainly by environmental factors. Obesity has recently been established as a risk factor of the internal environment, particularly among women. External environmental factors include various exposures related to lifestyle. Tobacco smoking, alcohol drinking, coffee and tea consumption, as well as regular use of aspirin and other non-steroidal anti-inflammatory drugs, have all been proposed to be risk factors for reflux. Previous population based studies, though limited in sample size, suggest that tobacco smoking and table salt intake seem to be risk factors for gastro-oesophageal reflux.

In the present, large scale, population based study we investigated the role of several lifestyle related exposures in the aetiology of symptomatic GORD. Our hypothesis was that tobacco smoking, alcohol, and coffee cause reflux, whereas dietary fibres and physical exercise may be protective. We further examined tea drinking and table salt intake, without having any biologically grounded hypothesis regarding these exposures.

METHODS

The HUNT public health surveys

In the Norwegian county of Nord-Trondelag, two extensive public health surveys have been conducted during recent decades. The first survey, Helseundersøkelsen i Nord-Trondelag 1 (HUNT 1) was performed in 1984–86 and included 74,599 individuals (representing 88.1% of the population) aged 20 years and above. Data for the second survey (HUNT 2) were collected in 1995–97. That survey included 65,363 individuals (representing 71.2% of the population) aged 20 years and above. A total of 47,556 individuals—72.8% of all HUNT 2 participants—participated in both surveys.

Exposures

At local temporary research centres, all participants completed extensive written questionnaires covering a wide variety of exposures. In the current study, we specifically analysed variables that were related to lifestyle. These variables included tobacco smoking, use of alcohol, dietary habits, as well as physical exercise. Furthermore, all participating subjects underwent a limited physical examination, including assessment of blood pressure, body weight, and height. In addition, age, sex, and body mass index (BMI; body weight in kilograms divided by the square of body height) were included in the analysis as confounding factors.

Abbreviations: GORD: gastro-oesophageal reflux disease; HUNT: Helseundersøkelsen i Nord-Trondelag; BMI: body mass index; OR: odds ratio
height in meters) were assessed as potential confounders. For the potential risk factors and confounders assessed, there were data from HUNT 2—that is, cross sectional data or, in the case of smoking, historic data of lifetime exposure. For alcohol use, table salt use, and physical exercise, there were data from both HUNT 1 (prospectively collected data) and HUNT 2 (cross sectional data). For these exposures, HUNT 1 data were used, in order to lessen the risk of bias from reversed causality—that is, that concomitant occurrence of reflux symptoms would influence the level of exposure.

### Definition of reflux disease
The outcome was defined as severe and recurrent heartburn or regurgitation: the cardinal symptoms of reflux.16–19 The outcome was assessed in the HUNT 2 survey only. The subjects answered a question concerning whether they had experienced heartburn or acid regurgitation during the past 12 months and, if so, whether the symptoms were minor or severe. Of the 58 596 people in the HUNT 2 survey (90%) that answered this question, 40 210 (69%) had had no such symptoms, 15 233 (26%) had had minor symptoms, and 3153 (5%) had experienced severe symptoms of reflux. The 3153 subjects reporting severe reflux symptoms were selected to represent the case group and the 40 210 without reflux symptoms were chosen as control subjects. The 15 233 with minor symptoms were excluded as this group was judged to be too heterogeneous, with considerable risk of misclassification of the outcome.

To evaluate the outcome among people reporting reflux symptoms, we conducted a validation study where the response to the outcome question as posed in the questionnaire was compared with responses to a more extensive reflux symptom questionnaire covering symptom frequency, duration, nightly symptoms, effect of antireflux medication, and impact of the symptoms on everyday life. Out of 1102 outpatients, included at general practitioners in Nord-Trøndelag, the community hospital of Levanger in Nord-Trøndelag, and at the Karolinska Hospital in Stockholm, 103 (10%) reported severe symptoms of heartburn or regurgitation during the past 12 months. In this group with severe symptoms, 72% reported heartburn or regurgitation occurring at least daily or being on daily antireflux medication, 23% had experienced the regurgitation once or several times per week, and 5% had symptoms less frequently than once weekly. Hence, 95% of the group corresponding to our case group had experienced reflux symptoms at least once per week during the preceding 12 month period. The specificity for symptoms occurring at least once per week in this “sample of cases” was 99.5% and the corresponding sensitivity was 58%. Among the 280 (25%) subjects who reported minor reflux symptoms in the validation study (corresponding to the group excluded from the study), 15% had daily symptoms or used antireflux medication on a daily basis, 10% had symptoms at least once per week, and 75% had symptoms less frequently than once a week. Hence, the majority of people in this sample of those excluded as cases or controls had reflux symptoms occurring less frequently than once per week.

### Statistical analyses
All variables under study were categorised to facilitate unconditional logistic regression analysis. The categories for the number of years of daily tobacco smoking (cigarette, pipe, or cigar) were <1 year (reference), 1–5 years, 6–10 years, 11–20 years, and >20 years. The lifetime total number of cigarettes smoked were grouped into <100 cigarettes (reference), 101–25 000, 25 001–50 000, 50 001–100 000, 100 001–200 000, and finally >200 000 cigarettes. The frequency of alcohol consumption, defined as the number of occasions on which wine, spirits, or beer had been consumed during the preceding two weeks (HUNT 1, prospectively collected data), were grouped into: none (reference), 1–4 occasions, 5–10 occasions, and >10 occasions. Estimated average daily coffee use (HUNT 2, cross sectional data) was categorised into <1 cup (reference), 1–3 cups, 4–7 cups, and >7 cups. Daily average tea use (HUNT 2, cross sectional data) was categorised into <1 cup (reference), 1–3 cups, >3 cups. Table salt use (HUNT 1, prospectively collected data) was assessed by two variables. Firstly, the average frequency of meals of salted fish or meat was categorised into never (reference), <3/month, once/week, twice/week, and > twice/week. Secondly, the average use of extra salt on regular meals was grouped into never (reference), sometimes, often, and always. Dietary fibre content (HUNT 2, cross sectional data), expressed as the dry weight percentage of the type of bread predominantly consumed, was categorised into plain white bread, 1–2% (reference); soft medium fibre bread, 4–7%; soft high fibre content bread, 6–10%; and finally hard bread, 14–16%. Regular physical exercise of at least 30 minutes duration (HUNT 1, prospectively collected data) was categorised into never (reference), <1/week, 1–3/week, and >3/week. BMI was categorised into <25, 25–30, 30–35, and >35 kg/m².

Odds ratios (OR) and their 95% confidence intervals (CI), derived from unconditional logistic regression, were used to assess the association between the potential risk factors under study and the risk of reflux symptoms.20 Linear trends of the associations were tested by treating categorical variables as continuous in the multivariate model. Potential confounding effects of age, sex, BMI, asthma medication, as well as all the exposure variables under study, were tested by introducing them one by one into the model.

Informed consent was obtained from all participants of the study. The study was approved by the Regional Committee for Medical Research Ethics, Region IV, Norway.

### RESULTS
#### Age and sex distribution
The age and sex distribution among the study subjects is presented in table 1. Mean ages were 52 years (case subjects) and 48 years (control subjects). There were no pronounced age differences between sexes.

#### Tobacco smoking and alcohol consumption
There was a moderately strong and dose dependent association between increasing duration of daily tobacco smoking of cigarettes, pipes, or cigars and risk of reflux symptoms (p value for linear trend <0.0001) (table 2). The multivariate analysis revealed that among individuals who had smoked daily for more than 20 years, the risk of reflux was significantly increased by 70%, compared with those who had smoked daily for less than a year (OR 1.7; 95% CI 1.5 to 1.9).

### Table 1 Age and sex distribution among cases with reflux symptoms and control subjects without reflux symptoms

<table>
<thead>
<tr>
<th></th>
<th>Men (%)</th>
<th>Women (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>1555 (7.4)</td>
<td>1598 (6.9)</td>
<td>3153 (7.3)</td>
</tr>
<tr>
<td>Cases</td>
<td>18814 (92.4)</td>
<td>21396 (93.1)</td>
<td>40210 (97.7)</td>
</tr>
<tr>
<td>Controls</td>
<td>50</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>48</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Cases</td>
<td>19–101</td>
<td>20–92</td>
<td>19–101</td>
</tr>
<tr>
<td>Controls</td>
<td>19–99</td>
<td>19–95</td>
<td>19–99</td>
</tr>
</tbody>
</table>
Likewise, there was a dose dependent association between the lifetime total number of cigarettes smoked and reflux symptoms (p value for linear trend = 0.0001) (table 2). Individuals who had smoked more than 50,000 cigarettes had a significant 60% increased risk of reflux symptoms compared with those who had smoked fewer than 100 cigarettes in the multivariate analysis (OR 1.6; 95% CI 1.4 to 1.8). Alcohol consumption, assessed in HUNT 1, and thus prospectively collected, was not associated with any change in the risk of reflux—independent of the level of consumption (table 2). For both tobacco smoking and alcohol consumption, the multivariately adjusted odds ratios were not markedly different from the unadjusted estimates, indicating lack of strong confounding effects by the variables included in the model (listed in the methods section).

### Dietary factors

Data on the use of coffee and tea were collected from the HUNT 2 survey only, and are therefore of cross sectional nature. In the multivariate analysis there was a negative association between coffee intake and reflux symptoms with added extra salt to regular meals. A moderate and dose dependent association between increasing frequency of meals of salted fish or meat and from how often the person drank more than seven cups of coffee per day, compared with those who drank less than one cup (OR 0.6; 95% CI 0.4 to 0.7). This finding differed markedly from the univariate analysis of coffee exposure, which showed a slight increase in risk of reflux when comparing the same groups as above (OR 1.2; 95% CI 1.1 to 1.4). The analyses revealed that the increased risk of reflux identified in the univariate data could be entirely explained by confounding from tobacco smoking. Tea drinking was not associated with any effect on the risk of reflux symptoms, independent of the adjustment for potential confounding variables (table 3).

The use of table salt, based on data from HUNT 1, and thus collected prospectively, was estimated from the frequency of meals of salted fish or meat and from how often the person never ate salted food (OR 1.5; 95% CI 1.2 to 1.8). Similarly, the increasing use of extra table salt on regular meals was associated with an increased risk of reflux in a dose dependent manner (p value for linear trend <0.0001). The risk of reflux among people who ate salted food three times per week or more was significantly increased by 50% compared with those who never ate salted food (OR 1.5; 95% CI 1.2 to 1.8). Similarly, the increasing use of extra table salt on regular meals was associated with an increased risk of reflux in a dose dependent manner (p value for linear trend <0.0001). The risk of reflux was 70% increased among people who always added extra salt compared with those who never did so (OR: 1.7; 95% CI 1.4 to 2.0) (table 3). With increasing dietary fibre content in the predominantly consumed bread type (HUNT 2; cross sectional data), the risk of reflux decreased significantly (p value for linear trend <0.0001) (table 3). People who predominantly ate bread with 7% dry weight of dietary fibres or more, had an approximately halved risk of having reflux symptoms compared with those who predominantly ate white, low fibre content (1–2%) bread (OR 0.5; 95% CI 0.4 to 0.7). No strong confounding effects were identified in the analyses of dietary salt or fibres (table 3).

### Physical exercise

Increasing frequency of physical exercise sessions (HUNT 1 data; prospectively collected) lasting at least 30 minutes, exemplified by jogging, cross country skiing, and exercise swimming, correlated with a decrease in risk of reflux symptoms (p value for linear trend <0.0001). Physical exercise once a week was associated with a significant, 50% decreased risk of reflux when compared with individuals who never did any organised physical exercise of at least 30 minutes duration (OR 0.5; 95% CI 0.4 to 0.7) (table 4). Univariate data did not markedly differ from the multivariate results, indicating limited influence of confounding factors.

### Table 2 Tobacco smoking, alcohol use, and risk of symptomatic gastro-oesophageal reflux

<table>
<thead>
<tr>
<th>Tobacco smoking†</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Daily smoking (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>1253</td>
<td>20414</td>
<td>1.0</td>
<td>(reference)</td>
<td>1.0</td>
<td>(reference)</td>
</tr>
<tr>
<td>1–5</td>
<td>133</td>
<td>2204</td>
<td>1.0</td>
<td>(0.8–1.2)</td>
<td>1.2</td>
<td>(0.9–1.6)</td>
</tr>
<tr>
<td>6–10</td>
<td>251</td>
<td>3000</td>
<td>1.4</td>
<td>(1.2–1.6)</td>
<td>1.5</td>
<td>(1.2–1.8)</td>
</tr>
<tr>
<td>10–20</td>
<td>540</td>
<td>5583</td>
<td>1.6</td>
<td>(1.4–1.8)</td>
<td>1.7</td>
<td>(1.4–1.9)</td>
</tr>
<tr>
<td>&gt;20</td>
<td>976</td>
<td>9009</td>
<td>1.8</td>
<td>(1.6–1.9)</td>
<td>1.7</td>
<td>(1.5–1.9)</td>
</tr>
<tr>
<td><strong>p Value for linear trend</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Lifetime number of cigarettes smoked (thousands) |       |          |     |        |     |        |
| <0.1             | 1391  | 21681    | 1.0 | (reference) | 1.0 | (reference) |
| 0.1–25           | 239   | 3744     | 1.0 | (0.9–1.1) | 1.1 | (0.9–1.4) |
| >25–50           | 296   | 3345     | 1.4 | (1.2–1.6) | 1.5 | (1.3–1.8) |
| >50–100          | 484   | 4968     | 1.5 | (1.4–1.7) | 1.6 | (1.4–1.8) |
| >100–200         | 520   | 4816     | 1.7 | (1.5–1.9) | 1.6 | (1.4–1.9) |
| >200             | 223   | 1656     | 2.1 | (1.8–2.4) | 1.6 | (1.3–2.0) |
| **p Value for linear trend** |       |          |     |        |     |        |

<table>
<thead>
<tr>
<th>Alcohol use†</th>
<th>Occasions of spirits, wine, or beer consumption during last two weeks</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1066 11960</td>
<td>1.0</td>
<td>(reference)</td>
<td>1.0</td>
<td>(reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>776   10029</td>
<td>0.9</td>
<td>(0.8–1.0)</td>
<td>0.9</td>
<td>(0.8–1.0)</td>
<td></td>
<td></td>
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<tr>
<td>5–10</td>
<td>58    695</td>
<td>0.9</td>
<td>(0.7–1.2)</td>
<td>0.9</td>
<td>(0.7–1.2)</td>
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<td></td>
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<tr>
<td>&gt;10</td>
<td>67    655</td>
<td>1.1</td>
<td>(0.9–1.5)</td>
<td>1.0</td>
<td>(0.8–1.3)</td>
<td></td>
<td></td>
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<tr>
<td><strong>p Value for linear trend</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*In the multivariate logistic regression model adjustments were made for age, sex, body mass index, tobacco smoking, alcohol use, coffee use, and asthma medication. Tea drinking, table salt intake, dietary fibre in bread, and physical exercise were tested in the model, but omitted from the final model because they did not contribute significantly to the explained variance.

†Tobacco smoking and alcohol use variables represent exposure previous to reflux outcome assessment.

OR, odds ratio; CI, confidence interval.
DISCUSSION

The present study indicates an important role for exogenous exposures in the form of lifestyle related factors in the aetiology of GORD. Exposures associated with an increased risk of reflux symptoms were tobacco smoking and the use of table salt. A reduced risk of reflux was found among people who drank large amounts of coffee, who ate bread high in dietary fibre content, and who frequently exercised. The consumption of alcohol or tea did not affect the risk of reflux.

Strengths of our study include the population based design and considerably smaller than the present study, have found that the specificity is still sufficiently high, compared with that of the other available methods, previous studies specificity of symptom evaluation might be lower, compared with more objective methods, such as pH measurement or endoscopy. This concern, however, is relieved by the fact that the symptoms used for outcome assessment, namely heartburn and acid regurgitation, are well validated as representative of true GORD. Actually, reflux symptoms are likely to be the best available measure of reflux disease in epidemiological studies. Although the specificity of symptom evaluation might be lower, compared with that of the other available methods, previous studies have found that the specificity is still sufficiently high, especially in subjects with frequent symptoms. Notably, the sensitivity of symptom evaluation is considerably higher than that of the alternative methods. Nevertheless, we separately evaluated the question concerning reflux symptoms in the HUNT 2 survey against a more extensive, previously used reflux symptom questionnaire, in a validation study. This validation confirmed that the question in the HUNT 2 survey identified people who indicated severe heartburn or regurgitation during the past 12 months (corresponding to the case definition in the main study), and who had at least weekly symptoms, with very high specificity (99.5%). Another potential source of error in our study. This validation confirmed that the question in the HUNT 2 survey identified people who indicated severe heartburn or regurgitation during the past 12 months (corresponding to the case definition in the main study), and who had at least weekly symptoms, with very high specificity (99.5%). Another potential source of error in our study is confounding, which was, however, thoroughly evaluated in our multivariate analyses.

Previous epidemiological studies, of cross sectional design and considerably smaller than the present study, have proposed a relation between tobacco smoking and reflux...
symptoms. Our study strongly suggests that tobacco smoking is a risk factor for reflux symptoms. The tobacco smoking data analysed in this study represent lifetime exposure, and are as such less vulnerable to reversed causality than the corresponding cross sectional exposure data would have been. The consistent dose response relations between both years of daily smoking, and lifetime total number of cigarettes smoked and reflux symptoms, provide convincing evidence that long term tobacco smoking is indeed a risk factor for symptomatic GORD. Experimental studies have shown a reduction of the lower esophageal sphincter pressure and increased frequency of reflux episodes during tobacco smoking,21–24 which may be the mechanism behind the association.

Similar to the situation for tobacco smoking, alcohol use has been shown to evoke reflux episodes,25 26 but data concerning long term effects and relation to pathological reflux are limited. The only previous study that, to our knowledge, directly addressed the issue concluded that alcohol use is a moderate risk factor for reflux symptoms. In the present study, which is larger, and in which alcohol exposure was assessed well ahead of reflux outcome measurement, we found no association between alcohol exposure and the risk of reflux symptoms. The relative risk estimates were generally close to one, independent of the level of alcohol consumption. Hence, our results strongly suggest a lack of association between alcohol and reflux.

Coffee has been reported to precipitate reflux episodes,27 28 but previous cross sectional epidemiological studies have not been able to establish that coffee drinking is a risk factor for GORD.29 30 In the present study, cross sectional coffee exposure data showed a reduced risk of reflux symptoms among coffee drinkers compared with non-coffee drinkers. Given that it is likely that coffee intake induces symptoms in some susceptible individuals, the risk reduction we observed might be explained by reversed causality: if individuals with reflux symptoms abstain from drinking coffee this would leave a selection of subjects without reflux symptoms among coffee drinkers. The effect of coffee exposure differed markedly when analysed univariately and multivariately, mainly because of positive confounding by smoking. To minimise the influence of reversed causality, and more accurately evaluate the long term effects of coffee drinking on the risk of reflux, an analysis of prospective exposure data would be necessary.

Tea drinking has previously only been studied in a case series of reflux esophagitis patients and experimentally as a risk factor for gastro-oesophageal reflux. In the present study, prospective data indicate a significant protective effect of regular, at least weekly, physical exercise of 30 minutes duration or more. The mechanism of this

<table>
<thead>
<tr>
<th>Physical exercise</th>
<th>Number</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>Controls</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>&lt;30 minutes duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>275</td>
<td>2231</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>&lt;1/week</td>
<td>233</td>
<td>3775</td>
<td>0.7 (0.5–0.8)</td>
</tr>
<tr>
<td>1/week</td>
<td>116</td>
<td>1432</td>
<td>0.7 (0.5–0.8)</td>
</tr>
<tr>
<td>≥3/week</td>
<td>116</td>
<td>1020</td>
<td>0.9 (0.7–1.2)</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.

The risk reduction we observed among coffee drinkers compared with non-coffee drinkers.

Given that it is likely that coffee exposure was assessed well ahead of reflux outcome measurement, we found no association between coffee exposure and the risk of reflux. The relative risk estimates were generally close to one, independent of the level of coffee consumption. Hence, our results strongly suggest a lack of association between coffee and reflux.

Coffee has been reported to precipitate reflux episodes,27 28 but previous cross sectional epidemiological studies have not been able to establish that coffee drinking is a risk factor for GORD.29 30 In the present study, cross sectional coffee exposure data showed a reduced risk of reflux symptoms among coffee drinkers compared with non-coffee drinkers. Given that it is likely that coffee intake induces symptoms in some susceptible individuals, the risk reduction we observed might be explained by reversed causality: if individuals with reflux symptoms abstain from drinking coffee this would leave a selection of subjects without reflux symptoms among coffee drinkers. The effect of coffee exposure differed markedly when analysed univariately and multivariately, mainly because of positive confounding by smoking. To minimise the influence of reversed causality, and more accurately evaluate the long term effects of coffee drinking on the risk of reflux, an analysis of prospective exposure data would be necessary.

Tea drinking has previously only been studied in a case series of reflux esophagitis patients and experimentally as a substance that might evoke reflux episodes,28 but no significant effect on reflux was seen in either of these studies. In light of these previous negative findings and the data from our present study, tea drinking does not seem to be a risk factor for GORD.

Table salt (sodium chloride) has to our knowledge not previously been evaluated as a risk factor for gastro-oesophageal reflux. In the study population from Nord-Trøndelag in Norway, heavily salted fish and meat dishes are an inherent part of the traditional diet, which provided us with an important table salt exposure variable not available in many other populations. The consistent dose response relations, between the frequency of eating salted foods and the risk of reflux symptoms, and between applying extra salt on regular meals and the risk of reflux, indicate that high table salt intake may be a true risk factor for symptomatic GORD. The validity of this association is augmented by the prospective nature of the table salt exposure data, though confounding by other, unknown dietary factors cannot be completely ruled out. As this study is the first to address the relation between salt and reflux, more studies are needed before an association can be established.

Dietary fibres, especially those of cereal origin, have been shown to be associated with a reduced risk of oesophageal and gastric cardia adenocarcinoma,29 tumours for which gastro-oesophageal reflux is the main risk factor.4 In the present study population, bread is one of the dominating sources of carbohydrates, with most individuals eating two meals per day based on bread. Our cross sectional data on dietary fibre content, of the predominantly consumed bread type, showed a dose-dependent reduction in risk of reflux symptoms with increasing fibre content, suggesting a protective effect against reflux. We can only speculate about the biological mechanism behind this finding. In the acidic environment of the stomach large amounts of nitric oxide are produced non-enzymatically from nitrates in the diet.31 Nitric oxide has a potent relaxing effect on the lower oesophageal sphincter,32–34 and is as such likely to promote reflux. Dietary fibres are well known to scavenge nitrates in the stomach,35–37 thereby decreasing the availability of the substrate for non-enzymatic nitric oxide synthesis. This might reduce nitric oxide concentration in the gastro-oesophageal junction, and thus prevent reflux. Given the cross sectional nature of the dietary fibre variable, reversed causality cannot be ruled out, although it seems unlikely as it presupposes that bread with a high fibre content would evoke reflux symptoms, and thus be avoided by reflux prone individuals, a phenomenon which has not been reported.

To our knowledge, the long term effect of physical exercise on the risk of GORD has not been addressed previously. In the present study, prospective data indicate a significant protective effect of regular, at least weekly, physical exercise of 30 minutes duration or more. The mechanism of this
protective effect could be by strengthening the crural diaphragm, thus possibly improving the function of the part of the antireflux barrier constituted by the striated muscle of the diaphragm. There was no dose response relation, which slightly lessens the credibility of the association. Further studies are needed before the role of physical exercise in reflux aetiology can be established.

In conclusion, our large, population based study provides firm evidence in support of our hypothesis that tobacco smoking causes symptomatic GORD, and some evidence that dietary fibres in bread and physical exercise protect against this disorder. The study further provides sound evidence against our hypothesis that alcohol use causes symptomatic reflux disease, and some evidence against coffee or tea being causally related to reflux. Moreover, our study generates a new hypothesis concerning table salt as a possible long term causal agent behind GORD.

ACKNOWLEDGEMENTS

We gratefully acknowledge the assistance of the following institutions: The Norwegian Institute of Public Health and the HUNT Research Centre, Verdal, Norway for performing the two HUNT surveys; The HUNT Research Centre, Verdal, Norway and the medical faculty of the Norwegian University of Science and Technology, Trondheim, Norway for allowing access to the database; and AstraZeneca, Sweden and The Swedish Medical Society for financial support.

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*Gut* 2004 53: 1730-1735
doi: 10.1136/gut.2004.043265

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