Obesity and Estrogen as Risk Factors for Gastroesophageal Reflux Symptoms

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Gastroesophageal reflux disease and obesity are both highly prevalent in Western societies, and the occurrence of these conditions is rapidly increasing.¹⁻⁷ Reflux has an adverse impact on quality of life,⁸ and the costs for long-term antireflux medication are high.⁹ Reflux symptoms¹⁰⁻¹² and obesity¹³,¹⁴ are strong and independent risk factors for esophageal adenocarcinoma, a cancer that has increased significantly in incidence during recent decades.¹⁵,¹⁶

The relation between body mass and gastroesophageal reflux symptoms remains uncertain, and valid data to assess this proposed association are limited. In our previous study, we demonstrated a strong and dose-dependent association between increasing body mass and endoscopically verified esophagitis in women, but no association was found in men.¹⁷ Moreover, the positive association among women seemed to be augmented by postmenopausal hormone therapy, suggesting a role of female sex hormones in the etiology of reflux disease.¹⁷

To examine the relation between body mass and reflux symptoms and evaluate the influence of female sex hormones, we conducted a large population-based, cross-sectional, case-control study.

Methods

The HUNT Public Health Surveys

In the Norwegian County of Nord-Trøndelag, 2 extensive public health surveys have been conducted during recent decades. The first, Helseundersøkelsen i Nord-Trøndelag 1 (HUNT 1), was performed in 1984-1986 and included 74599 individuals, representing 88.1% of the entire adult population. The second survey, HUNT 2, conducted in 1995-1997, included 65363 individuals, representing 71.2% of the adult population. A total of 47556 individuals, representing 72.8% of all persons included in HUNT 2, participated in both surveys.

Context  Gastroesophageal reflux and obesity are both increasing in prevalence. The scientific evidence for an association between these conditions is sparse and contradictory. A difference between sexes concerning this relation has been proposed.

Objective  To evaluate the relation between body mass and gastroesophageal reflux symptoms and determine how this relation is influenced by female sex hormones.

Design  Population-based, cross-sectional, case-control study.


Participants  Among 65363 adult participants in the second survey, 3113 individuals who reported severe heartburn or regurgitation during the last 12 months were defined as cases, whereas 39872 persons without reflux symptoms were defined as controls.

Main Outcome Measure  Risk of reflux, estimated using multivariate logistic regression, with odds ratios (ORs) and 95% confidence intervals (CIs) as measures of association.

Results  There was a dose-response association between increasing body mass index (BMI) and reflux symptoms in both sexes (P for trend <.001), with a significantly stronger association in women (P < .001). Compared with those with a BMI less than 25, the risk of reflux was increased significantly among severely obese (BMI > 35) men (OR, 3.3; 95% CI, 2.4-4.7) and women (OR, 6.3; 95% CI, 4.9-8.0). The association between BMI and reflux symptoms was stronger among premenopausal women compared with postmenopausal women (P < .001), although use of postmenopausal hormone therapy increased the strength of the association (P < .001). Reduction in BMI was associated with decreased risk of reflux symptoms.

Conclusions  There is a significant association between body mass and symptoms of gastroesophageal reflux. The association is stronger among women, especially pre-menopausally, and use of hormone therapy strengthens the association, suggesting that estrogens may play an important role in the etiology of reflux disease.

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**Exposures and Definition of Reflux**

At their local health centers, all participants completed extensive written questionnaires that covered a wide variety of exposures. A total of 813 variables were included in both surveys together. Data were collected on defined disorders and diseases, lifestyle factors, behavioral habits, work and employment information, use of medications, and aspects of psychosocial well-being. Furthermore, all participants underwent certain physical examinations, including assessment of body weight and height, and BMI18 (weight in kilograms divided by the square of height in meters) was calculated based on objective measurements. Information on other exposures of interest, including present or previous postmenopausal hormone therapy, menstrual status, and previous hysterectomy, was gathered in the questionnaire.

**Definition of Reflux Disease**

The outcome was defined as severe symptoms of reflux (eg, recurrent heartburn or regurgitation) and was assessed in HUNT 2 only. Participants answered a question regarding whether they had experienced heartburn or regurgitation during the past 12 months and, if so, if the symptoms were minor or severe. Among the 58,996 persons (90%) in the HUNT 2 survey who answered this question, 40,210 (69%) reported that they had had no reflux symptoms, 15,233 (26%) had had minor symptoms, and 3,153 (5%) had experienced severe symptoms of reflux. The 3,153 individuals who reported severe symptoms were selected to represent the case group and the 40,210 persons without reflux symptoms were selected as controls. The 15,233 persons with minor symptoms were analyzed separately, because the symptom pattern in this group was considered to be heterogeneous, with an increased risk of misclassification of the outcome, compared with the group reporting severe symptoms.

Heartburn and acid regurgitation are the cardinal symptoms of gastroesophageal reflux disease, and the use of questionnaires to assess these symptoms is well validated as a reliable measurement of the true occurrence of reflux.10-22 To further evaluate the outcome among persons who reported different levels of reflux symptoms in the HUNT 2 survey, we conducted a separate validation study. The question that covered reflux symptoms used in HUNT 2 was compared with a more extensive, validated questionnaire that covered the frequency and duration of reflux symptoms, the occurrence of nightly reflux symptoms, the use and effect of specified antireflux medications, and the effect of the reflux symptoms on everyday life. A total of 1,102 outpatients at general practices in Nord-Trøndelag, the community hospital of Levanger in Nord-Trøndelag, and the Karolinska Hospital in Stockholm, Sweden, were included in the validation study.

**Statistical Analyses**

The cutoff points for BMI were predetermined and based on the World Health Organization classification of overweight and obesity.23 A BMI value between 25 and 30 is defined as overweight, a BMI greater than 30 as obesity, and a BMI greater than 35 as severe obesity. All persons with a BMI value less than 25 (normal) constituted the reference group in comparisons between BMI levels. Odds ratios (ORs) and their 95% confidence intervals (CIs), derived from unconditional logistic regression, were used to assess the association between BMI and the risk of reflux.24 Linear trend of the association was tested in a multivariate model by treating categorical variables as continuous.

Potential confounding effects of age (in 10-year intervals), tobacco smoking (years of daily smoking subdivided into <1 year, 1-10 years, and >10 years), alcohol drinking (number of alcoholic beverages consumed during the 2 weeks preceding data collection, subdivided into 0, 1-4 drinks, 5-10 drinks, and >10 drinks), asthma medication (months of daily use during the last 12 months), antihypertensive medication (present use), diabetes mellitus (known diagnosis), coffee use (cups per day), tea use (cups per day), table salt use (extra salt on regular meals), and dietary fiber intake (predominantly consumed type of bread classified in terms of dietary fiber content) were controlled by introducing these variables individually into the model. For asthma medication, antihypertensive medication, coffee and tea use, and dietary fiber in bread, data were available from HUNT 2 only. For the other potential confounders, data were available from both surveys. Whenever possible, data from HUNT 1 or HUNT 2 for lifetime exposure were used rather than cross-sectional HUNT 2 data to reduce the risk of reversed causality (ie, that the level of exposure is affected by the occurrence of reflux symptoms). Moreover, nonspecific gastrointestinal symptoms, such as nausea (during last 12 months), constipation (minor or severe during last 12 months), and diarrhea (minor or severe during last 12 months) were tested as outcome variables in the logistic regression model (ie, as control symptoms for reflux).

The potential interaction effect (ie, effect modification) between body mass and hormone therapy was tested by introducing a cross-product term, representing the interaction between the 2 variables, into the model. To avoid confounding effects from pregnancy, women who reported that they were pregnant at the time of the HUNT 2 reflux outcome assessment were excluded from further analysis. To investigate differences in the risk of reflux related to BMI between premenopausal and postmenopausal women, data from female study participants were stratified according to menstrual status and then entered into the multivariate model. The effects of weight loss and weight gain were assessed by entering the net change in BMI between the HUNT 1 and HUNT 2 surveys into the model, with adjustment for baseline BMI (ie, the BMI measured in the HUNT 1 survey). Informed consent was obtained from all participants in the study. The study was approved by the Re-
OBESITY, ESTROGEN, AND GASTROESOPHAGEAL REFLUX

Regional Committee for Medical Research Ethics, Region IV, Norway.

RESULTS

Characteristics of the Study Participants

In total, the study evaluated 43,363 subjects (20,369 men and 22,994 women). After excluding 378 pregnant women, 22,616 women remained for further analysis. Some general characteristics of the participants are presented in Table 1. The mean age of the participants was 52 years among the 3113 cases and 48 years among the 39,872 controls. The age differences between sexes were minor and not significant. Mean BMI was 28.1 among cases and 25.8 among controls. Among female cases, 14.8% had ever used hormone therapy, whereas the corresponding frequency was 9.6% among the female controls.

BMI and Reflux Symptoms

Among men, a moderate and dose-dependent association between increasing BMI and reflux symptoms was observed in the multivariate analysis (P for trend <.001) (Table 2). Severely obese men (BMI >35) demonstrated a more than 3-fold increase in risk of reflux symptoms (OR, 3.3; 95% CI, 2.4-4.7) compared with men of normal weight (BMI <25). The corresponding analysis among severely obese (BMI >35) women revealed a similarly dose-dependent but stronger association compared with that observed in men (P <.001) (Table 2), with a more than 6-fold increase in risk of reflux symptoms (OR, 6.3; 95% CI, 4.9-8.0) compared with women of normal weight (BMI <25). Adjustment for age only revealed no major differences compared with the multivariate analyses, indicating lack of important confounding by the variables that were tested (data not shown).

Influence of Menopause and Hormone Therapy

The association between BMI and reflux symptoms was stronger in severely obese postmenopausal women than in severely obese postmenopausal women (P <.001) (Table 2) (OR, 6.8; 95% CI, 4.7-9.7; and OR, 4.2; 95% CI, 3.2-5.3, respectively) compared with women of normal weight with the same menstrual status.

Among women who had ever (presently or previously) been treated with hormone therapy, there was a strong and dose-dependent increase in the risk of reflux symptoms, especially in the highest BMI intervals, representing mainly an effect modification (P <.001) of the BMI effect on risk of reflux symptoms (Table 3). The separate effect (independent of obesity) of hormone therapy was tested among women of normal weight (BMI <25), and a tendency toward increased risk of reflux among women who ever

Table 1. Characteristics of Participants With Reflux Symptoms (Cases) and Without Reflux Symptoms (Controls)*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone therapy, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters using Helseundersøkelsen i Nord-Trøndelag 2 (HUNT 2) data.

Table 2. Association Between Obesity and Risk of Reflux Symptoms*

<table>
<thead>
<tr>
<th>BMI†</th>
<th>&lt;25</th>
<th>25-30</th>
<th>&gt;30-35</th>
<th>&gt;35</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>317</td>
<td>916</td>
<td>271</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>No. of controls</td>
<td>7378</td>
<td>9151</td>
<td>1926</td>
<td>289</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.0 (Referent)</td>
<td>2.2 (2.0-2.6)</td>
<td>3.1 (2.6-3.6)</td>
<td>3.3 (2.4-4.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>401</td>
<td>612</td>
<td>365</td>
<td>159</td>
<td></td>
</tr>
<tr>
<td>No. of controls</td>
<td>10,558</td>
<td>7402</td>
<td>2245</td>
<td>687</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.0 (Referent)</td>
<td>2.0 (1.7-2.4)</td>
<td>3.9 (3.3-4.7)</td>
<td>6.3 (4.9-8.0)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Postmenopausal Women

| OR (95% CI) | 1.0 (Referent) | 1.9 (1.6-2.3) | 3.2 (2.6-4.0) | 4.2 (3.2-5.5) | <.001 |

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

In the multivariate logistic regression model, adjustments were made for age, tobacco smoking, asthma medication, and postmenopausal hormone therapy in women. Alcohol use, antihypertensive medication, diabetes mellitus, coffee and tea use, table salt use, and intake of dietary fibers in bread were tested in the model but omitted in this presentation since they did not have any significant confounding effects. Pregnant women were excluded from analysis. BMI data were missing in 280 participants. Menopause status data were missing in 1687 participants (7.3%). BMI was calculated as weight in kilograms divided by the square of height in meters using Helseundersøkelsen i Nord-Trøndelag 2 (HUNT 2) data.
received hormone therapy was found but was not statistically significant (OR, 1.3; 95% CI, 0.9-1.8). In the group of women treated with hormone therapy after hysterectomy (ie, women without an endometrium to protect who hence received estrogens only [without gestagens]), the risk of reflux in normal-weight women was increased significantly (OR, 2.3; 95% CI, 1.1-4.8) (Table 3).

The risk of reflux symptoms was increased among women with BMI greater than 35 currently using hormone therapy and among women in the same BMI category with previous hormone therapy. The highest risk of reflux symptoms observed in our study was among women treated with estrogen-only hormone therapy (ie, previous hysterectomy) with a BMI greater than 35, although the number of women in these groups was small (Table 3). In general, the age-adjusted estimates did not differ importantly from the estimates from multivariate models (data not shown).

### BMI Data From the HUNT 1 Survey and Analysis of Weight Changes

For the 72.8% of the individuals who participated in both surveys, we repeated the analyses using BMI data from the first survey (ie, approximately a decade before the assessment of reflux symptoms). A weak association between increasing body mass and reflux symptoms was found among moderately obese men (BMI 30-35), with a 40% increase in risk of reflux symptoms (OR, 1.4; 95% CI, 1.1-1.9) compared with men of normal weight (BMI <25). Among severely obese men (BMI >35), the association was not statistically significant (OR, 1.8; 95% CI, 0.9-3.5).

In women, the association was stronger, with a significant increase in the risk of reflux symptoms in all 3 categories of overweight and obesity compared with those with a BMI less than 25. Overweight nonpregnant women (BMI 25-30) had an increased risk of reflux symptoms compared with participants with a BMI less than 25 (OR, 2.1; 95% CI, 1.7-2.4). In obese women (BMI 30-35) the risk of reflux symptoms was increased compared with women of normal weight (OR, 3.2; 95% CI, 2.3-4.1), and the corresponding risk was similarly increased in severely obese women (BMI >35) (OR, 2.5; 95% CI, 1.7-4.0). The analyses concerning exposure to hormone therapy based on data from HUNT 1 are similar to the results from HUNT 2, although the strength of the associations are somewhat diluted. Both analyses show strong and dose-dependent increases in risk of reflux symptoms among hormone therapy users. Similar to the results from HUNT 2, the strongest association was among severely obese women (BMI >35) taking estrogen-only hormone therapy.

### Table 3. Risk of Reflux Symptoms Among Women in Different BMI Categories, Including Status of HT

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Never HT</th>
<th>Ever HT</th>
<th>Present HT</th>
<th>Previous HT</th>
<th>Ever HT, posthysterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>253</td>
<td>45</td>
<td>32</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>25-30</td>
<td>347</td>
<td>101</td>
<td>58</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>&gt;30-35</td>
<td>200</td>
<td>58</td>
<td>34</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>&gt;35</td>
<td>92</td>
<td>32</td>
<td>21</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>All BMI Categories</td>
<td>892</td>
<td>236</td>
<td>144</td>
<td>92</td>
<td>41</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; HT, hormone therapy; OR, odds ratio.

*In the multivariate logistic regression model, adjustments were made for age, tobacco smoking, and asthma medication. Alcohol use, antihypertensive medication, diabetes mellitus, coffee and tea use, table salt use, and intake of dietary fibers in bread were tested in the model but omitted in this presentation since they did not have any significant confounding effects. The far right column was, in addition to the adjustments mentioned herein, also adjusted to BMI. P value for interaction term between BMI and HT never-ever status was <.001.

BMI was calculated as weight in kilograms divided by the square of height in meters using Helseundersokelsen i Nord-Trondelag 1 (HUNT 1) data. [Ref: BMI = weight (kg) / height (m)^2]

†Referent for all ORs presented in the table except for last column (concerning all BMI categories).

§Referent for ORs presented in the last column.

[Posthysterectomy status indicates HT with estrogens only (no gestagens).]
Participants in both surveys were evaluated for the association between weight change, identified during the time interval between the 2 surveys, and risk of reflux (Table 4). The risk of reflux was dose-dependently greater with increasing net BMI gain. In the group that gained more than 3.5 BMI units, the risk of reflux symptoms was increased (OR, 2.7; 95% CI, 2.3-3.2) compared with persons with stable BMI, whereas the risk of reflux symptoms was decreased among persons who lost more than 3.5 BMI units (OR, 0.6; 95% CI, 0.4-0.9).

**Additional Analyses**

Sex-stratified analyses of the relation between BMI and reflux symptoms and analyses of the influence of hormone therapy were also performed using the 15,233 study participants who reported minor reflux symptoms (omitted from the main analyses because of suspected heterogeneity of symptoms) as the case group, instead of persons who reported severe symptoms. The results of these analyses were similar, except with lower point estimates and weaker trends, compared with the analyses using severe reflux outcome for case classification (data not shown).

In analyses of the association between BMI and hormone therapy and control symptoms for reflux, the risks of nausea, constipation, and diarrhea were not significantly affected by either variations in BMI or use of hormone therapy (data not shown).

**Validation Study of Reflux Symptoms**

In the validation study, which comprises a total of 1102 participants, 103 (9.6%) reported severe reflux symptoms of heartburn or regurgitation during the past 12 months. In this group (which corresponded to our case group with severe reflux symptoms), 72% reported heartburn or regurgitation that occurred at least daily or were taking antireflux medication daily, 23% had heartburn or regurgitation one 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. Among the 280 participants (25.4%) who reported minor symptoms of heartburn or acid regurgitation during the past 12 months (corresponding to the group excluded from the main analyses), 15% had daily symptoms or had 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. Among those reporting severe reflux symptoms (corresponding to the case group in the main analyses), the specificity for symptoms that occurred at least once per week was 99.5% and the corresponding sensitivity was 58.3%.

**COMMENT**

This study demonstrates a strong and dose-dependent association between increasing body mass and symptomatic reflux in women and a moderate association among men. The association was stronger among premenopausal women. There was a weak association between hormone therapy and reflux in women of normal weight. With increasing body mass, the association between hormone therapy and reflux became increasingly stronger, suggesting that hormone therapy is an effect modifier of the association between body mass and reflux. The study also reveals that weight loss is associated with reduced risk of reflux symptoms.

Strengths of the study include the population-based design with high participation rates, reducing the risk of selection bias. The large sample size decreased the risk of chance findings and facilitated extensive subgroup analyses. The wide range of exposure data made it possible to adjust for potential confounding variables.

A weakness of the study is that reflux was assessed only in the HUNT 2 survey, which prevented us from assessing new cases of reflux that occurred between the 2 surveys (ie, truly incident cases). This cross-sectional design theoretically opens the field for reversed causality. However, the consistently strong and dose-dependent associations among body mass, hormone therapy, and reflux symptoms, together with the biological implausibility of reflux causing obesity and the use of hormone therapy, provide reassurance against reversed causality.

Another possible weakness is that reflux was assessed by reflux symptoms only, with a potential risk of misclassification of the outcome. This is of less concern, however, because the symptoms used for outcome assessment, heartburn and regurgitation, are well validated as representing true reflux disease. Furthermore, we validated our question concerning reflux symptoms against a more extensive, previously used reflux symptom questionnaire. The usual definition of reflux disease, based on symptom evaluation, is a frequency of symptoms of once per week.

### Table 4. Association of Weight Change Between the 1984-1986 and 1995-1997 Surveys and Risk of Gastroesophageal Reflux Symptoms *

<table>
<thead>
<tr>
<th>Weight Loss, BMI Units†</th>
<th>Weight Gain, BMI Units†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Weight Change</td>
<td>0.5-1.5 &gt;1.5-3.5 &gt;3.5</td>
</tr>
<tr>
<td>No. of cases</td>
<td>290 98 81 69</td>
</tr>
<tr>
<td>No. of controls</td>
<td>4628 1684 1097 928</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>1.0 (Referent) 0.8 (0.7-1.1) 0.9 (0.7-1.2) 0.6 (0.4-0.9)</td>
</tr>
<tr>
<td></td>
<td>1.2 (1.0-1.4) 1.6 (1.4-1.8) 2.7 (2.3-3.2)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

*In the multivariate logistic regression model, adjustments were made for baseline (1984-1986) BMI, age, and sex.

†BMI was calculated as weight in kilograms divided by the square of height in meters using Helseundersøkelsen Nord-Trøndelag 1 (HUNT 1) and HUNT 2 data.
or more. In the validation study, 95% of the group corresponding to our case group had reflux symptoms that fulfilled this definition, confirming our outcome assessment to have high specificity (99.5%). Moreover, any misclassification of reflux would dilute the associations and could not explain the positive associations. The fact that the analyses of the participants who reported minor reflux symptoms revealed similar but weaker patterns of associations compared with the main analyses of persons with severe reflux symptoms further supports the credibility of our results.

All analyses used BMI data from the HUNT 1 and HUNT 2 surveys. Results were similar, revealing the same patterns of associations, but in data from HUNT 1 the point estimates were generally weaker. This difference between the surveys is probably because the relation between BMI and reflux is more dependent on current than previous BMI. In this respect, current, cross-sectional BMI data may be more relevant to reflux outcome than previous BMI.

Previous scientific evidence concerning the relation between body mass and reflux is ambiguous. Three population-based, epidemiological studies have evaluated the association between body mass and reflux symptoms. In our previous cross-sectional study of reflux symptoms, we found no association. In light of the data presented herein, that might be explained by the low percentage (17%) of women included and that BMI was assessed retrospectively at least 20 years before the collection of data. Previous (as opposed to present) exposure to high BMI levels diluted the results in the present study, particularly among men. This could explain the negative result in our previous study. In a cross-sectional study, Locke et al9 identified a moderate association, but no separate analysis of men and women was presented. In a cohort design, Ruhl and Everhart demonstrated a weak association between BMI and hospitalization for reflux diagnoses. Our previous population-based study examining the relation between body mass and endoscopically verified that reflux esophagitis demonstrated a strong and dose-dependent association between increasing body mass and reflux esophagitis in women, augmented by hormone therapy, whereas no association was found in men. The difference between our previous study and the present study, concerning the association among men, might be explained by lack of precision in the previous study.

The findings of our previous report led us to formulate the hypothesis that estrogen might be involved in the pathogenesis of reflux disease among obese women. The concentration of sex hormone–binding globulin is lower among obese women than normal-weight women, resulting in a larger proportion of unbound, active estradiol. Moreover, obese women also have increased synthesis of estrone in the fatty tissue. Reflux symptoms during pregnancy usually commence during the first trimester because of a predominately hormonally mediated pathogenesis, and women taking sequential oral contraceptives have reduced lower esophageal sphincter tone, facilitating reflux. Moreover, estrogen increases nitric oxide synthesis, the predominant relaxing transmitter substance of the lower esophageal sphincter, resulting in smooth muscle relaxation in animal models and humans. Therefore, we hypothesize that the association between estrogens and reflux might be conveyed by a nitric oxide–mediated reduction of smooth muscle tone in the lower esophageal sphincter. Findings from a randomized, double-blind, crossover, placebo-controlled study showing that nitric oxide synthesis increased with increasing BMI in postmenopausal women with estrogen treatment support this hypothesis. Our finding that hormone therapy increases the risk of reflux with increasing degrees of obesity supports a role of female sex hormones in the etiology of reflux disease. Furthermore, the finding that stratification for estrogen-only hormone therapy is the only significant effect of hormone therapy on reflux risk among normal-weight women (BMI <25) and the strongest effect among severely obese women (BMI >35) suggests that the hormone therapy effect is mediated by estrogens and not gestagens.

Stratification between present and previous use of hormone therapy reveals a stronger effect modification of the BMI effect on reflux symptoms among previous hormone therapy users than among present users. This finding might be explained by selection bias in that individuals who had reflux symptoms before hormone therapy might have had exacerbation of symptoms during present hormone therapy and therefore may have stopped treatment. Such bias does not affect the “ever hormone therapy” group as a whole, because it only affects the distribution between the present and previous groups. The finding that weight loss, manifested as a reduction in BMI between the 2 surveys, was associated with a significantly decreased risk of reflux symptoms when compared with individuals with stable BMI supports the role of weight loss in the clinical management of patients with reflux symptoms.

In conclusion, our large, population-based study provides evidence of a dose-dependent association between increasing body mass and the risk of gastroesophageal reflux symptoms. Hormone therapy was a weak risk factor for reflux symptoms but increased the strength of the association between body mass and reflux, an effect that was more pronounced with estrogen-only treatment. Weight reduction is associated with reduced risk of reflux.

**Author Contributions:** Drs Nilsson, Ye, and Lagergren had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Nilsson, Johnsen, Ye, Hveem, Lagergren.

**Acquisition of data:** Nilsson, Johnsen, Hveem.

**Analysis and interpretation of data:** Nilsson, Johnsen, Ye, Hveem, Lagergren.

**Drafting of the manuscript:** Nilsson, Johnsen, Hveem, Lagergren.

**Critical revision of the manuscript for important intellectual content:** Nilsson, Johnsen, Ye, Hveem, Lagergren.

**Statistical expertise:** Nilsson, Johnsen, Ye.

** Obtained funding:** Nilsson, Lagergren.

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