Mortality associated with moderate intakes of wine, beer, or spirits

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Abstract

Objective—**To examine the association between intake of different types of alcoholic drinks and mortality.**

Design—**Prospective population study with baseline assessment of alcohol intake, smoking habit, income, education, and body mass index, and 10-12 years' follow up of mortality.**

Setting—**Copenhagen city heart study, Denmark.**

Subjects—**6051 men and 7234 women aged 30-70 years.**

Main outcome measure—**Number and time of cause-specific deaths from 1976 to 1988.**

Results—**The risk of dying steadily decreased with an increasing intake of wine—from a relative risk of 1·00 for the subjects who never drank wine to 0·51 (95% confidence interval 0·32 to 0·81) for those who drank three to five glasses a day. Intake of neither beer nor spirits, however, was associated with reduced risk. For spirits intake the relative risk of dying increased from 1·00 for those who never drank to 1·34 (1·05 to 1·71) for those with an intake of three to five drinks a day. The effects of the three types of alcoholic drinks seemed to be independent of each other, and no significant interactions existed with sex, age, education, income, smoking, or body mass index. Wine drinking showed the same relation to risk of death from cardiovascular and cerebrovascular disease as to risk of death from all causes.**

Conclusion—**Low to moderate intake of wine is associated with lower mortality from cardiovascular and cerebrovascular disease and other causes. Similar intake of spirits implied an increased risk, while beer drinking did not affect mortality.**

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Introduction

During the past decade several large population studies have shown a U shaped relation between alcohol intake and mortality for both men and women throughout adulthood.[1-6] In a recent study we found that the U shape persisted when the effects of other risk factors, such as smoking and obesity, were controlled for.[7] Furthermore, neither a higher prevalence of disease at baseline nor an increased number of former drinkers among non-drinkers can explain the U shape.[7,8] The risk function for all cause mortality may be the result of combined effects of a decreasing risk of coronary heart disease and an increasing risk of cirrhosis, cancers, and violent deaths, due to an increasing intake.[4] St Leger and colleagues[9] and more recently Renaud and colleagues[10] found an inverse relation between incidence of coronary heart disease and wine consumption in different countries but no such relation for beer consumption. This suggests that the type of alcoholic drink, in addition to alcohol itself, influences the risk of heart disease. Some studies have addressed the issue of type of drink and death from heart disease but did so rather superficially and gave conflicting results.[11-17] In a recent paper specifically addressing this question Klatsky and Armstrong suggested that people who drink wine may be better protected against death from coronary heart disease than those who drink other alcoholic beverages, but proper risk functions were not estimated.[18]

We assessed the effects of different types of alcoholic drinks on the risk of death from all causes and from cardiovascular and cerebrovascular disease, while taking into account sex, age, socioeconomic conditions, smoking habits, and body mass index.

Subjects and methods

POPULATION

The study population comprised a random, age stratified sample of 19 698 out of 87 172 individuals aged 20 or more living in the Østerbro area of Copenhagen in 1976. During 1976-8 the Copenhagen city heart study examined by questionnaire 14 223 subjects (6511 men, 7712 women; response rate 72·2%). A detailed description of the study procedure has been published previously.[19] The present analysis concerns a sample of 13 285 subjects (6051 men, 7234 women) aged 30-79.

EXAMINATION PROCEDURES

The subjects filled in a self administered questionnaire about various issues related to health, including alcohol intake, smoking habits, school education, and household income. Weight in light clothes and height without shoes were measured, and from these the body mass index (weight(kg)/(height(m)^2)) was calculated.

Alcohol intake—The subjects were asked in multiple choice form whether they drank beer (bottles), wine (glasses), or spirits (units) "hardly ever/never," "monthly," "weekly," or "daily." If a subject drank alcohol daily then he or she had to report the average number of drinks of each type taken each day. One bottle of beer contains 12 g of alcohol, and this may be considered the average for the other types of drinks. If a subject abstained from drinking alcohol because he or she was receiving treatment (for example, disulfiram) or because of dipsomania (n=17) then this was noted, and the subject was excluded from the analysis.

Smoking habits—The subjects reported if they had never smoked, were former smokers, or current smokers. Former smokers were divided into groups according to duration (in years) of non-smoking, and current smokers according to amount of tobacco (in grams smoked each day). For the analysis five groups were defined: subjects who had never smoked; former smokers who had not smoked for more than five years; former smokers who had not smoked for five years or less; smokers of 1-19 g tobacco daily; smokers of more than 19 g daily.

FOLLOW UP

We followed the survival of the population sample until 1 January 1988, using the unique person identification number in the national central person register. We obtained causes of death, as recorded on death certificates, from the National Board of Health. Death from cardiovascular and cerebrovascular disease was defined according to the *International Classification of Diseases*, eighth revision, as codes 410.0 to 445.9. Each subject was observed from their initial examination (1976-8) until 1 January 1988, or until death (2229), disappearance (one), or emigration (39) if these occurred earlier.

STATISTICAL ANALYSIS

Data were analysed with multiple Poisson regression models.[20] The mortality was assumed to be constant within each 10 year age interval. A subject who was observed in more than one age group contributed with corresponding observation time in both groups. Further details of the model analysis have been described previously.[7]

The model included subjects' age, sex, and intakes of beer, wine, and spirits and the first order interactions between these variables. Each type of alcoholic drink was classified as never drunk; drunk monthly; drunk weekly; one to two drinks a day; or three to five drinks a day. Subjects having more than five drinks a day of beer, wine, or spirits were excluded from this analysis because there were too few cases in some of the groups (see table I). Exclusion of subjects who had more than five drinks a day of one type of alcoholic drink meant that some subjects who had less than five drinks daily of the other types were excluded. In this model first order interactions were tested. The criterion for inclusion was significance at the 5% level. We added the following covariates to this reduced model: smoking, body mass index, school education, and income. These were added one by one for separate testing.

In another model, the risk of dying as a function of reported intake at baseline was estimated separately for the first six years and the second six years. For detailed description of the statistical methods, we refer to the recently published statistical appendix.[7]

Results

Table I shows the distribution of subjects according to the different types of alcoholic drink. Some subjects who never drank alcohol of one type drank one or two of the others. Thus 1116 subjects never drank beer but did drink wine or spirits, 1245 never drank wine but did drink beer or spirits, and 860 never drank spirits but did drink beer or wine. In all, 5858 subjects drank both wine and beer, 5408 drank both spirits and wine, and 4629 drank both spirits and beer. Only 77 subjects drank wine, beer, and spirits every day. A total of 2120 women and 625 men never drank any alcohol.

During follow up 831 women and 1398 men died; 354 of the women and 765 of the men died from cardiovascular or cerebrovascular disease. The number of deaths analysed was reduced by 275 owing to exclusion of subjects who had more than five drinks of one type of alcohol. In the models for all cause mortality and mortality from cardiovascular or cerebrovascular disease including age, sex, smoking, and intake of beer, wine, or spirits all first order interactions—except interaction between age and sex—were not significant. Thus intake of beer, wine, or spirits appeared independently associated with mortality in this population. Estimates are reported from the models including all three types of alcoholic drinks.

Smoking was a confounder as the subjects who drank any type of alcoholic drink were more likely to smoke than those who did not drink at all, and smoking influenced mortality. The reported results are therefore controlled for smoking. We found no significant effect, however, of education, income, or body mass index on the relation between any of the types of drink and mortality.

WINE INTAKE AND MORTALITY

The wine drinkers experienced a significantly lower all cause mortality than the subjects who drank no wine. When relative risk was set at 1·00 for subjects who never drank wine the risk steadily decreased to 0·51 (95% confidence interval 0·32 to 0·81) for subjects who drank three to five glasses of wine a day (figure). The risk of death from cardiovascular and cerebrovascular disease declined from 1·00 for non-drinkers to 0·4 (0·24 to 0·80) for drinkers of three to five glasses of wine a day (table II). With regard to causes of death other than cardiovascular and cerebrovascular disease, drinking wine implied a decreased risk compared with not drinking wine (table II).

BEER INTAKE AND MORTALITY

We found no trend in all cause mortality in relation to the subjects who drank beer daily compared with the subjects who never drank beer, but we found a slight, significant decrease in risk among those who drank beer monthly. The relative risk was 0·96 (0·86 to 1·07) for subjects who drank beer weekly and 0·95 (0·83 to 1·09) for those who drank three to five beers a day (figure). With respect to death from cardiovascular and cerebrovascular disease, intake of three to five

TABLE I—*Distribution of alcohol intake and number of deaths from all causes and from cardiovascular and cerebrovascular disease in 13 285 subjects aged 30-79 years, by sex and type of alcoholic drink*

	Men			Women		
Alcoholic drink	Total No of persons	Total No of deaths	Deaths from cardiovascular and cerebrovascular disease	Total No of persons	Total No of deaths	Deaths from cardiovascular and cerebrovascular disease
Beer:						
Never	987	286	164	3738	499	228
Monthly	1123	221	138	1931	161	61
Weekly	1521	293	165	1123	114	41
Daily:						
One to two drinks	1126	288	161	378	50	21
Three to five drinks	881	200	90	54	6	3
More than six drinks	413	110	47	10	1	0
Wine:						
Never	2553	780	421	3037	473	234
Monthly	2304	433	241	2820	251	91
Weekly	930	134	72	1046	84	21
Daily:						
One to two drinks	195	42	24	256	19	7
Three to five drinks	62	8	6	68	4	1
More than six drinks	7	1	1	7	0	0
Spirits:						
Never	2305	617	336	4062	523	229
Monthly	2241	388	216	2193	198	76
Weekly	992	219	120	688	66	23
Daily:						
One to two drinks	361	118	65	254	40	25
Three to five drinks	152	56	28	37	4	1
More than six drinks	0	0	0	0	0	0
Total	6051	1398	765	7234	831	354

TABLE II—*Relative risk (95% confidence interval) of death from coronary heart disease and from other causes, as function of reported intake of alcoholic drinks by 13 285 subjects aged 30-79 years*

Frequency of drinking	Beer intake	Wine intake	Spirits intake
Death from cardiovascular and cerebrovascular disease:			
Never	1·00 (reference)	1·00 (reference)	1·00 (reference)
Monthly	0·79 (0·69 to 0·91)	0·69 (0·62 to 0·77)	0·95 (0·85 to 1·06)
Weekly	0·87 (0·75 to 0·99)	0·53 (0·45 to 0·63)	1·08 (0·93 to 1·26)
Daily:			
One to two drinks	0·79 (0·68 to 0·91)	0·47 (0·35 to 0·62)	1·16 (0·98 to 1·39)
Three to five drinks	0·72 (0·61 to 0·88)	0·44 (0·24 to 0·80)	1·35 (1·00 to 1·83)
Other causes of death:			
Never	1·00 (reference)	1·00 (reference)	1·00 (reference)
Monthly	0·82 (0·71 to 0·95)	0·86 (0·77 to 0·97)	0·80 (0·71 to 0·91)
Weekly	1·02 (0·89 to 1·18)	0·75 (0·64 to 0·88)	0·92 (0·79 to 1·08)
Daily:			
One to two drinks	0·96 (0·84 to 1·15)	0·80 (0·62 to 1·03)	0·81 (0·65 to 0·99)
Three to five drinks	1·22 (1·02 to 1·45)	0·50 (0·27 to 0·91)	1·36 (1·01 to 1·84)

beers a day implied a reduction in risk of 0·72 (0·61 to 0·88) compared with not drinking beer (Table II).

SPIRITS INTAKE AND MORTALITY

As with wine and beer, monthly intake of spirits was associated with a slight, significant decrease in risk, but drinking spirits weekly or once or twice a day did not influence all cause mortality compared with not drinking spirits at all. An intake of three to five drinks a day, however, was associated with a significantly increased risk of 1·34 (1·05 to 1·71) compared with not drinking spirits (figure). The risk function between intake of spirits and mortality from cardiovascular and cerebrovascular disease showed the same pattern as the one for all cause mortality (table II).

STABILITY OF RISK FUNCTIONS

The analysis was repeated with the observation time divided into the first and second six year periods. The increased mortality among subjects who did not drink wine compared with those who drank wine daily persisted in the second period.

Discussion

We clearly distinguished the different types of alcoholic drinks with respect to their relation to all cause mortality and mortality from cardiovascular and cerebrovascular disease. We found that the descending part of the U shaped curve describing the relation between alcohol and mortality could be explained almost exclusively by the effect of drinking wine. Furthermore, our study showed that the first part of the ascending curve—the increasing mortality among heavy drinkers—may be explained primarily by the effect of drinking spirits.

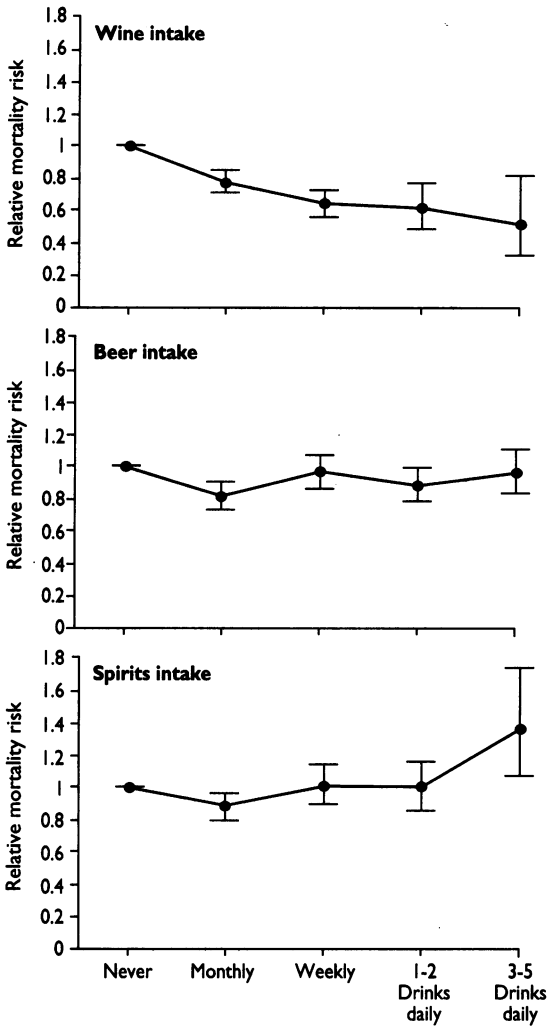
VALIDITY OF REPORTED INTAKE

The validity of self reported alcohol intake may be questioned, but no other available methods (such as sales reports, collateral information) have proved to be more valid.[21] We have no reason to believe that drinkers of one type of alcoholic drink report their intake differently from drinkers of other types. If underreporting takes place, as is commonly assumed, then this would lower the estimated health damaging effect of spirits, moving the "true" threshold of hazardous drinking to the right. On the other hand, the estimated beneficial effect of wine, if it were related to an even greater intake, would appear even more striking. Thus if underreporting takes place the estimated beneficial effect of, say, three to five glasses of wine a day, would relate to a greater intake. The results may therefore be considered conservative estimates of the true differences in the effects of the different drinks.

We found no excess mortality among subjects who did not drink beer or spirits. Of course, the presence of sick non-drinkers could mask a possible beneficial effect of not drinking beer or spirits. For wine drinking, the presence of sick non-drinkers would contribute to the inverse risk function. We also analysed, however, the mortality risk function in the first and second six years of follow up and found no changes between the two periods. Furthermore, only a fraction of non-drinkers of one of the three types of drink were also non-drinkers of the other two types. Sick non-drinkers are probably not, therefore, imposing an important bias on the results.

ANALYSES OF EFFECTS OF TYPE OF ALCOHOLIC DRINKS

The descending part of the U shaped curve describing the relation between alcohol and mortality has been attributed to a protective effect of ethanol, but the question of type of alcoholic drink has been addressed rather superficially. Some studies have mentioned having controlled for, or by other means included, the type of drink in the analysis—with no or little difference in effect on mortality.[11-16] Others have addressed the question specifically, but may have had too small a material or too little variance in intake of the different drinks to detect differences.[1 17 22] An ecological study reported that it is apparently an advantage, with respect to coronary heart disease, to live in a country of wine drinkers rather than in a country of drinkers of beer or spirits.[10] This finding was supported by Klatsky and Armstrong, who indicated that people who preferred wine may have a lower risk of dying from coronary heart disease.[18] Klatsky and Armstrong grouped subjects according to preference of a given type of drink. This might have led to loss of information as well as misclassification because



Relative risk, with confidence interval, of mortality in relation to intake of wine, beer, and spirits. The risk is set at 1·00 for subjects who never drank

many subjects presumably drank two or all three types of drink. Klatsky and Armstrong's method of classification might also have hindered comparison between drinkers of different types of drinks and the group of non-drinkers of each type of drink.

An important difference between the studies mentioned above and our study is that we specifically addressed not only the question of separate effects of the different types of alcoholic drinks on mortality but also the question of possible interactions between the types of alcoholic drinks on mortality. A remarkable methodological advantage in conducting the study in Denmark is that the Danes, in contrast with people in countries with a more uniform pattern of drinking or a culture of non-drinking, drink some of all types of alcoholic drink, which enabled us to create the five intake groups for wine, beer, and spirits. Drinking one type of alcohol will affect the pattern of drinking another. The statistical model should therefore include all three types of alcohol. We found no significant interaction between the three types of alcoholic drinks and could therefore provide estimates of independent effect of each type (ranging from never drinking to having three to five drinks daily of that type) on mortality.

The left limb of the U shaped curve has been the subject of much debate. A prevailing belief is that the non-drinkers constitute a mixture of former heavy drinkers, drinkers who underreport, sick people who have stopped drinking, and people with a particularly unhealthy lifestyle apart from not drinking. As seen in table I, for each of the three types of drink, quite a large group of subjects were non-drinkers. Patients taking disulfiram and patients with dipsomania were excluded from the analysis. The influence of type of drink on mortality seemed to show that the drinks were statistically independent of each other, and the difference persisted throughout the 12 years of follow up. Smoking is known to confound the estimates of the effect of alcohol intake on mortality,[7] and we therefore controlled for this factor. We found that wine intake was positively correlated with social class variables (data not shown), but the protective effect of wine, with regard to mortality, was not significantly weakened when we controlled for this factor. Sex, age, and body mass index did not confound our results either. Residual confounding by some of the included variables or by other, unknown confounders may none the less have occurred. To explain the effect, however, such confounders would have to exhibit a peculiar distribution across the range of intakes of the three types of drinks. If a variable, such as physical activity, were a confounder (assuming that physical activity reduces mortality) then there should be an increase in physical activity by increased wine intake, decreased activity by increased spirits intake, and no change in relation to beer. Moreover, the effect of any such potential confounder should be very strong to explain our findings.

POSSIBLE PROTECTIVE FACTORS IN WINE APART FROM ETHANOL

The results strongly suggest that, in addition to the common effect of ethanol, there are—within the studied range of drinking—different factors influencing health in the three types of drink. Specifically, the results raise the question of what might be the protective agent in wine or the damaging factors in beer and spirits apart from ethanol. The decreased mortality in cardiovascular and cerebrovascular disease among beer drinkers may reflect a common effect of ethanol on high density lipoprotein or fibrinolytic factors.[23] Furthermore, an inverse relation has been found between alcohol intake and platelet aggregability,[24] and, in agreement with our results, this relation has been shown to be even stronger for wine.[25] Our finding, that only wine drinking clearly reduces both the risk of dying from cardiovascular and cerebrovascular disease and the risk of dying from other causes, suggests that other more broadly acting factors in wine may be present. Antioxidants and flavonoids, which are presumed to prevent both coronary heart disease and some cancers,[26,27] may be present in red wine. It has also been suggested that tannin and other phenolic compounds in red wine may have a protective effect.[28,29]

The number of drinks indicating the lowest risk on the alcohol-mortality risk function, as well as the thresholds of safe drinking, differs from study to study, and this variation may be due to differences between countries with regard to type of drinks consumed.

During the past 15 years mortality from coronary heart disease has declined by about 30% in Denmark.[30] This decrease cannot be ascribed to a rise in alcohol intake, which has been more or less stable during that period. On the other hand, with the opening of the European market, drinking patterns have changed quite dramatically in favour of wine drinking. In 1975 wine contributed to 17·3% of the total alcohol intake, rising to 30·2% in 1992,[31] which, in accordance with our findings, may have contributed to the decline in death from coronary heart disease.

In conclusion, our study shows that light and moderate wine drinking, in contrast with beer and spirits drinking, is associated with a strong dose dependent decrease in all cause mortality, attributable to a decrease in mortality from cardiovascular and cerebrovascular disease as well as from other causes. The biological mechanism behind the different effects of the three types of drinks needs further research.

Key messages

- The U shaped relation between alcohol intake and all cause mortality has been ascribed to the beneficial and harmful effects of ethanol
- Alcohol in small doses is assumed to protect against ischaemic heart disease
- In this study drinkers of three to five glasses of wine a day had half the risk of dying as those who never drank wine
- Beer and spirit drinkers experienced no such advantages, and three to five drinks of spirits a day was associated with increased mortality
- The U shaped risk function may be a result of a combination of the risk functions of wine, beer, and spirits

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Acyclovir given as prophylaxis against oral ulcers in acute myeloid leukaemia: randomised, double blind, placebo controlled trial

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Abstract

***Objectives*—To evaluate *(a)* the prophylactic effect of the antiherpetic drug acyclovir on oral ulcers in patients with acute myeloid leukaemia receiving remission induction chemotherapy and thus *(b)*, indirectly, the role of herpes simplex virus in the aetiology of these ulcers.**

***Design*—Randomised, double blind, placebo controlled trial.**

***Subjects*—74 herpes simplex virus seropositive patients aged 18-84. Thirty seven patients received acyclovir (800 mg by mouth daily) and 37 placebo. The patients were examined daily for 28 days.**

***Main outcome measures*—Occurrence of herpes labialis, intraoral ulcers, and acute necrotising ulcerative gingivitis.**

***Results*—The two populations were comparable in age, sex, type of antineoplastic treatment, and history of herpes labialis. Acute oral infections occurred in 25 of the acyclovir treated patients and 36 of the placebo treated patients (relative risk 0·69 (95% confidence interval 0·55 to 0·87)). This difference was due to a reduction in the incidence of herpes labialis (one case versus eight cases; relative risk 0·13 (0·02 to 0·95)), intraoral ulcers excluding the soft palate (one case versus 13 cases; relative risk 0·08 (0·01 to 0·56)), and acute necrotising ulcerative gingivitis (one case versus eight cases; relative risk 0·13 (0·02 to 0·95)). However, ulcers on the soft palate were diagnosed with similar frequency in the two groups. Isolation of herpes simplex virus type 1 in saliva was reduced from 15 cases in the placebo group to one case in the acyclovir group (relative risk 0·07 (0·01 to 0·48)).**

***Conclusion*—Intraoral ulcers excluding the soft palate are most often due to infection with herpes simplex virus, whereas ulcers on the soft palate have a non-herpetic aetiology. The findings suggest that acute necrotising ulcerative gingivitis may also be due to herpes simplex virus. Prophylaxis with acyclovir should be considered for patients with acute myeloid leukaemia during remission induction therapy.**

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Introduction

Acute myeloid leukaemia has remained a serious disease with a three year survival of only 15-20% after chemotherapy.[1] Further intensification of treatment is limited by chemotherapy induced side effects, in particular increased susceptibility to infection. Consequently, improvement in our ability to diagnose, treat, or prevent these complications is essential to allow further intensification of chemotherapy and thus achieve a reduction in the morbidity and mortality among these patients. Acute oral infections are frequent and clinically important in these patients. During feverish episodes they occur with an incidence of 75%, similar to the overall incidence of non-oral infections.[2] In particular, oral infections are the possible origin of septicaemia in about one third of cases.[3] Acute oral infections often present as oral ulcers.[4] These can be divided into herpes labialis, intraoral ulcers outside the gingival margin, and acute necrotising ulcerative gingivitis.

Herpes labialis is found in about 15% of an unselected group of patients with haematological disorders undergoing one chemotherapeutic treatment cycle.[4] This is similar to the prevalence in the background population.[5] Typically, the clinical picture of herpes labialis is comparable to that seen in healthy people, and overall the condition represents neither a diagnostic nor an aetiological problem in patients with haematological disorders. In contrast, intraoral ulcers outside the gingival margin occur in only 3% of healthy people,[5] whereas the incidence is as high as 30% in haematological patients during a chemotherapeutic treatment cycle.[4] The aetiology of intraoral ulcers is