particularly with regard to the question whether their symptoms truly originate from reflux of gastric contents. Indeed, what are judged "reflux symptoms" does not necessarily imply that these are due to GORD, as they may also occur in conditions such as functional heartburn and functional dyspepsia. Reduction of reflux episodes with a new drug will not result in symptom reduction in these latter patients.

Secondly, when one has ascertained that a patient's symptoms are indeed caused by gastro-oesophageal reflux, it is pivotal to treat the patient for a sufficient period of time. The effect of a PPI on acid secretion is within days but due to acid-induced oesophageal hypersensitivity the number of responders seems to increase for up to 8 or even 12 weeks of acid suppressive treatment.^{2,3} Compliance to drug intake may be an issue when symptoms do not resolve immediately after onset of therapy. When symptoms persist even after a sufficiently long treatment period, either the drug does not adequately inhibit acid secretion and a higher dose is required, or the symptoms are induced by weak levels of acid (above pH 4), or the non-acid component of the reflux in which the only option would be a reduction of reflux episodes (by pharmacotherapeutic or surgical means).⁴ These patients are the ones that can be identified by impedance monitoring as Mainie *et al.* show in their study. These are also the patients that would benefit from a future reflux-reducing drug.

We conclude that a critical approach is required when symptoms do not respond adequately to PPI therapy in suspected GORD patients. The true number of PPI-refractory GORD patients is likely to be overestimated.

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Menopausal status and hepatic steatosis in a general female population

Population-based studies showed that non-alcoholic hepatic steatosis is less common in women than in men. Anti-oestrogens double the risk of non-alcoholic steatohepatitis,¹ which may be interpreted as indirect evidence for a protective role of endogenous oestrogens against steatohepatitis. Experimental evidence further suggests that oestradiol causes a reduction of hepatic steatosis in mice unable to produce oestrogens.² We thus hypothesised that the menopause as a natural state of oestrogen deficiency might increase the risk of hepatic steatosis.

The Study of Health in Pomerania is a cross-sectional population-based survey in northeast Germany.³ We restricted our analyses to 808 women aged 40-59 years without seropositivity to hepatitis B antigen and anti-hepatitis C virus. The study was approved by the ethics committee of the University of Greifswald. All participants gave written informed consent.

Menopause was defined as 12 consecutive months of amenorrhoea or cessation of menstruation after iatrogenic intervention. Serum

glutamate oxaloacetate transaminase, glutamic pyruvic transaminase and γ glutamyl transpeptidase levels were measured photometrically. Levels exceeding the 75th centile for each marker were considered to be raised. In liver ultrasound, a hypoechoic pattern was defined as the presence of a bright pattern with contrast between hepatic and renal parenchyma.⁴ Hepatic steatosis was defined as the presence of a hypoechoic ultrasound pattern and at least two raised levels among three serum transaminase levels. Multivariable statistical analyses were performed by logistic regressions. Sets of confounders were defined using directed acyclic graphs.⁵

Descriptive statistics showed the association between menopausal status and liver-related characteristics, which remained stable after adjustment for age (table 1). A first sufficient set of covariables included age, smoking and unmeasured confounders (fig 1A). Controlling analyses for age and smoking only marginally affected the relationship investigated (table 1, model 1). In a second directed acyclic graph (fig 1B), alcohol use and nutritional factors were further assumed as determinants of hepatic steatosis and also included in the sufficient set of covariables. This extended model did not substantially affect the association of interest (table 1, model 2). Model 2 was then supplemented by covariables without using any causal diagrams. These analyses gave non-conclusive results (table 1, model 3). Exclusion of all women with alcohol consumption >20 g/day ($n = 122$; 15.1%) changed the major results only marginally.

Our findings are in good agreement with a Korean ultrasound study⁶ in which the menopause was also a determinant of hepatic steatosis in women. Our results are further consistent with analyses of the National Health and Nutrition Examination Survey III.⁷ Non-alcoholic hepatic steatosis as defined by increased concentrations of liver enzymes was twice as common in postmenopausal as in premenopausal women.⁷

Oestrogens lead to a preferential fat accumulation in the gluteofemoral region⁸ and, conversely, the loss of oestrogens during menopause transition is associated with an increase in central fat.⁹ In obese women with hepatic steatosis, liver volumes correlate highly with visceral adipose tissue.¹⁰ The relationship between menopausal

Table 1 Relationship between menopausal status and liver-related characteristics

	Hypoechoic liver pattern	Raised serum GOT	Raised serum GPT	Raised serum GGT	Hepatic steatosis
Menopause, crude	2.41 (1.71 to 3.38)*	2.38 (1.68 to 3.36)*	2.53 (1.80 to 3.57)*	1.61 (1.16 to 2.24)*	5.88 (4.34 to 7.95)*
Menopause, adjusted for age	1.70 (1.1 to 2.61)*	1.75 (1.12 to 2.72)*	2.13 (1.37 to 3.31)*	1.62 (1.06 to 2.48)*	2.51 (1.57 to 4.02)*
Menopause, adjusted for model 1	1.71 (1.11 to 2.63)*	1.79 (1.14 to 2.79)*	2.15 (1.38 to 3.36)*	1.55 (1.01 to 2.38)*	2.51 (1.56 to 4.02)*
Menopause, adjusted for model 2	1.71 (1.11 to 2.64)*	1.78 (1.14 to 2.78)*	2.14 (1.37 to 3.33)*	1.56 (1.01 to 2.41)*	2.47 (1.54 to 4)*
Menopause, adjusted for model 3	1.45 (0.87 to 2.39)	1.67 (1.04 to 2.68)*	2.01 (1.23 to 3.26)*	1.43 (0.90 to 2.28)	1.93 (1.13 to 3.31)*

GGT, γ glutamyltransferase; GOT, glutamic-oxaloacetic transaminase; GPT, glutamic-pyruvic transferase.

Logistic regression analysis. Data are OR (95% CI).

Model 1 included age and smoking status (three categories) as sufficient set of confounders as defined from the causal diagram in fig 1.

Model 2 included age, smoking status (three categories), nutrition (three categories) and alcohol consumption (three categories) as defined from an alternate causal diagram in fig 2.

Model 3 included variables of model 2 and, in addition, body mass index (three categories), diabetes, use of menopausal hormone treatment, increased waist-to-hip ratio as well as increased serum low-density lipid cholesterol and plasma fibrinogen levels.

Hepatic steatosis was defined as the presence of a hypoechoic liver pattern in ultrasound and at least two among three characteristic raised serum GOT, GPT or GGT levels.

* $p < 0.05$.

Figure 1 Causal diagram for the association between menopause and hepatic steatosis. (A) A minimum set of confounders would include age, smoking status and unmeasured confounders such as common genetic factors. (B) In contrast with (A), the diagram considers additional causal effects of alcohol consumption and nutrition on menopausal status (dotted arrows). In this scenario, a minimum set of confounders would include age, smoking status, nutritional factors, alcohol consumption and unmeasured confounders such as common genetic factors.

status and hepatic steatosis found in our study may thus reflect the changes in fat distribution during menopausal transition.

Causal diagrams enable the accurate selection of covariables from a variety of potential variables influencing the studied association. It has been shown that an arbitrary inclusion of variables in multivariable models may not only lead to an underestimation of the association of interest but also introduce bias in the analyses.⁵ According to our directed acyclic graphs, metabolic factors should be regarded as mediators rather than confounders for the relationship investigated.

We conclude that menopausal status is associated with hepatic steatosis. The prognostic relevance of this association with respect to incident cardiovascular disease and diabetes has to be proved.

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Association between *Helicobacter pylori* infection and interleukin 1 β polymorphism predispose to CpG island methylation in gastric cancer

Interleukin1 β (IL1 β) is upregulated in the presence of *Helicobacter pylori* infection.¹ IL1 β polymorphisms with T/T and T/C genotypes enhance IL1 β production, and are associated with an increased risk of *H. pylori*-induced hypochlorhydria² and gastric cancer.³ The relationship between *H. pylori* and CpG island methylation has been repeatedly reported.^{4–6} It has been reported that IL1 β can modulate CpG island methylation through activation of DNA methyltransferase and hence repress gene expression.⁷ We therefore hypothesised that patients with *H. pylori* infection and IL1 polymorphism, by the production of IL1 β , are predisposed to gastric cancer development through the CpG island methylation pathway.

We obtained surgical specimens and their corresponding peripheral blood from 98 consecutive patients with gastric cancer admitted to Queen Mary Hospital, Hong Kong. This study was approved by the ethics committee. The methylation status of the death-associated protein-kinase, O⁶-methyl-guanine methyl-