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# Obesity, overweight and liver disease in the Midspan prospective cohort studies

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## Abstract

**Objectives—**To investigate the relationship between BMI and liver disease in men and women.

**Design—**The Midspan prospective cohort studies.

**Participants—**The three studies were: Main, screened 1965-8, workplaces across Scotland, the general population of the island of Tiree and mainland relatives; Collaborative, conducted from 1970-3, 27 workplaces in Glasgow, Clydebank and Grangemouth; Renfrew/Paisley general population study, screened in 1972-6. After exclusions there were 16 522 men and 10 216 women, grouped by body mass index (BMI) into under/normal weight (< 25 kg/m$^2$), overweight (25 to < 30 kg/m$^2$) and obese (≥ 30 kg/m$^2$).

**Measurements—**Relative rates (RR) of liver disease mortality, subdivided into liver cancer and all other liver disease, by BMI category and per standard deviation (SD) increase in BMI, followed-up to end 2007. RRs of liver disease from any diagnosis on the death certificate, hospital discharge records or cancer registrations (Collaborative and Renfrew/Paisley studies only 13 027 men and 9 328 women). Analyses adjusted for age and study, then other confounders.

**Results—**146 men (0.9%) and 61 women (0.6%) died of liver disease as main cause. There were strong associations of BMI with liver disease mortality in men (RR per SD increase in BMI=1.41 (95% confidence interval (CI) 1.21 to 1.65)). Obese men had more than three times the rate of liver disease mortality than under/normal weight men. Adjustment for other risk factors had very little impact. No substantial or robust associations were seen in women. 325 men (2.5%) and 155

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women (1.7%) had liver disease established from any source. Similar positive associations were seen for men, and there was evidence of a relationship in women.

**Conclusions—**BMI is related to liver disease, although not to liver disease mortality in women. The current rise in overweight and obesity may lead to a continuing epidemic of liver disease.

### Keywords

Liver disease; overweight; obesity; prospective cohort studies; Scotland



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## Introduction

Current unprecedented increases in the occurrence of liver disease are of considerable public health significance1, especially since rates of other chronic conditions, such as cardiovascular disease, are decreasing2. In Scotland, deaths from chronic liver disease have increased rapidly since the mid-1990s1; 3. Although the increase in alcohol consumption is thought to be one of the underlying factors, a role for increasing levels of obesity has also been postulated4. In 2003, almost 64% of Scottish men and 57% of Scottish women were overweight or obese, a marked increase from 1995 when the prevalences were 57% and 47% respectively5. Liver disease of metabolic origin associated with obesity is the most prevalent liver disease in Western countries6 and liver cancer mortality rates in the UK are predicted to rise by 14% in the next 20 years7.

Most previous studies have been limited to liver disease sub-types. It has been established that body mass index (BMI) is related to liver cancer, as shown in a meta-analysis8. Other studies have examined the role of BMI in the aetiology of specific causes of non-cancer liver disease, such as cirrhosis9. More recently, a study of male British civil servants has investigated all liver disease, reporting positive relationships between BMI and liver disease mortality10. In that study, data were only available for working men and only for mortality. The current study has been able to contribute to further understanding of the relationship between BMI and liver disease, by utilising both liver disease morbidity and mortality, and examining women as well as men, in a large data set. It includes three of the Midspan prospective cohort studies, which have participants from both the working and general population11.

## Methods

The Midspan studies began in the 1960s with a study known as “Main”, which included employees in several workplaces across the central belt of Scotland, the population of the island of Tiree and their relatives on the mainland11; 12. Participants were aged from 14 to 92 years at screening and, unusually for that time period, included both men and women. The study was conducted between 1965 and 1968. The second Midspan study, known as the Collaborative study was conducted on employed men and women aged from 21 to 75 years from 27 workplaces in Glasgow, Clydebank and Grangemouth between 1970 and 197313. The third Midspan study, the Renfrew/Paisley study, was a general population study of residents of the towns of Renfrew and Paisley, conducted between 1972 and 197614. All residents aged 45 to 64 years were invited to take part, and 80% accepted.

Protocols were very similar across the studies. They each consisted of a self-completed questionnaire followed by a screening examination, conducted at a specially set-up clinic. The questionnaire included questions on occupation, smoking habit, bronchitis, angina and diabetes. At the screening examination, measurements were made for blood pressure and forced expiratory volume in 1 second (FEV1) and an electrocardiogram (ECG) was taken. In the Renfrew/Paisley and Collaborative studies, a blood sample was taken for measurement

of plasma cholesterol. Height and weight were reported in the questionnaire in the Main study, but in the later Collaborative and Renfrew/Paisley studies, they were measured at the clinic.

Social class was derived from occupation according to the relevant version of the General Register Office Classification of Occupations (1960 for Main15, 1966 for Collaborative and Renfrew/Paisley16). Women who classified themselves as housewives in the Main or Renfrew/Paisley studies were allocated the social class of their husbands or fathers. Social class was graded in six categories: I (professional), II (intermediate), III non-manual (skilled non-manual), III manual (skilled manual), IV (partly skilled) and V (unskilled). Manual social class was defined as social class III manual, IV or V. Ex-smokers reported giving up smoking at least a year before screening. Smoking was defined by number of cigarettes smoked per day for current and ex-smokers. Bronchitis was defined by responses to the MRC bronchitis questionnaire17 and angina according to the Rose questionnaire18. Presence of diabetes was taken from a positive response to a question. At the screening examination, blood pressure was measured with a London School of Hygiene sphygmomanometer with the participant seated. FEV1 was measured using a Vitalograph spirometer, with the participant standing. Ischaemia on ECG was defined as any of Minnesota codes 1.1-1.3, 4.1-4.4, 5.1-5.3 and 7.119.

BMI was calculated from weight (in kg) divided by height squared (in $m^2$) and categorised according to WHO categories underweight (< 18.5 $kg/m^2$), normal weight (18.5 to < 25 $kg/m^2$), overweight (25 to < 30 $kg/m^2$) and obese (≥ 30 $kg/m^2$).

Follow-up after screening was by flagging with the NHS Central Register. Dates of deaths and their causes, as well as embarkations from the UK are notified monthly to the Midspan team. In addition, the Collaborative and Renfrew/Paisley studies have been linked with the Scottish Morbidity Records (SMR) data. These records were available from 1972. Any occurring before each individual's date of screening were excluded. The Privacy Advisory Committee of NHS Scotland Information Services gave permission for the linked data to be used in the current study on obesity and liver disease. Records used were from the SMR1 series of acute hospital discharges and the SMR6 series of cancer registrations.

Liver disease was defined as ICD9 codes 155 (liver cancer) and 570-573 (diseases of liver), and ICD10 codes C22 (liver cancer) and K70-K77 (diseases of liver) & subdivided into liver cancer (ICD9 155 and ICD10 C22) and all other liver disease (remaining codes). Mortality from liver disease was defined as having one of these causes as the underlying (main) cause of death. Follow-up was from the date of screening to the date of death, date of embarkation or 31$^{st}$ December 2007, whichever came first (median follow-up 26 years, maximum 42 years).

A further analysis defined having liver disease if the participant had an SMR1 with any of the diagnosis codes being liver disease, or an SMR6 for liver cancer, or had liver disease mentioned in any of the causes of death. Follow-up was to the date of the first occurring of the SMR1, SMR6, death, date of embarkation or 31$^{st}$ December 2007. This analysis was only possible for the Collaborative and Renfrew/Paisley studies as the SMR data were not available for the Main study.

The total numbers of participants in the three studies were Main 4 691 (3 750 male and 941 female), Collaborative 7 028 (6 022 male, 1 006 female) and Renfrew/Paisley 15 402 (7 049 male, 8 353 female), giving a total of 27 121(16 821 male, 10 300 female). Given the geographical proximity of the study populations, there were some individuals who took part in two studies (157 in Main and Collaborative, 26 in Collaborative and Renfrew/Paisley and 56 in both Main and Renfrew/Paisley). Data for these individuals were used only once: the

Collaborative or Renfrew/Paisley data were taken in preference to Main (height and weight were measured not self-reported), and the Collaborative utilised in preference to the Renfrew/Paisley data (the Collaborative study was conducted first).

The 69 Main participants who were aged under 18 at screening were excluded as they would not have achieved an "adult" BMI. Other exclusions were 10 Collaborative and 23 Renfrew/Paisley participants who were lost to follow-up and 31 Main, 1 Collaborative and 15 Renfrew/Paisley participants with missing BMI. Of the 31 Main participants with missing BMI, 5 were duplicates so their data were available in one of the other studies. In total there were 26 738 participants included in the study (16 522 male and 10 216 female). In the analyses using just the Collaborative and Renfrew/Paisley studies, there were 22 355 participants (13 027 male and 9 328 female).

## Statistical analysis

All analyses were conducted using Stata (release 10). Age-adjusted means and percentages were standardised by six age groups (<45, 45-49, 50-54, 55-59, 60-64, >64) for men and women separately.

There were 360 participants in the underweight category (126 male and 234 female). Since there was only one death from liver disease in the underweight category, this category was combined with the normal weight category. Sub-group analyses were also conducted after excluding underweight participants. Participants known to have embarked (Main 10, Collaborative 61 and Renfrew/Paisley 121) were censored at the date of embarkation. Cox Proportional Hazard models were used to obtain relative rates of mortality from liver disease (or having liver disease) by BMI category and for one standard deviation (SD) increase in BMI. The baseline category was taken as the under/normal weight category. Tests to check the proportional hazards assumption used Schoenfeld residuals. In the analyses of having liver disease, the proportional hazards assumption was not satisfied in the full follow-up period, but was satisfied over the first 28 years of follow-up. Test for interaction with sex were suggestive of different effects (p=0.015 for liver disease mortality) thus all analyses were performed for men and women separately. Tests for interaction with study did not provide strong evidence of difference (p=0.08 for men, p=0.78 for women for liver disease mortality). There was little evidence of a quadratic trend with BMI (p=0.87 for men, p=0.55 for women for liver disease mortality).

The proportional hazards models were first adjusted for age at screening and study, and were then adjusted for other risk factors (social class, smoking [cigarettes/day with an additional term to denote ex-smokers], systolic blood pressure, height, bronchitis, FEV1, angina, ischaemia on ECG and diabetes: also cholesterol for the analysis involving the Collaborative and Renfrew/Paisley studies only). Missing values of these risk factors were substituted with the study and sex-specific means.

The mortality analyses were repeated after excluding deaths and embarkations in the first five years of follow-up, as participants with pre-existing liver disease may have had lower than usual BMIs at screening. This could lead to underestimation of the association of BMI with liver disease mortality.

## Results

Of the men in the three studies, 45% were overweight and 8% were obese at screening, while 35% of the women were overweight and 14% obese (table 1). Risk factors were generally highest in obese men and women, with the main exception being current smoking which was lowest in the obese.

In the follow-up period, 146 men (0.9%) and 61 women (0.6%) died of liver disease as the main cause, 49 and 20 respectively of these deaths being due to liver cancer (table 2). There were strong associations of BMI with liver disease mortality in men (relative rate (RR) adjusted for age and study, associated with one standard deviation (SD) increase in BMI=1.41 (95% confidence interval (CI) 1.21 to 1.65)). Obese men had more than three times the rate of liver disease than under/normal weight men. Adjusting for other risk factors attenuated the relative rates only slightly. Similar results were seen for the subcategories of liver cancer and the remaining causes of liver disease. There was no strong evidence of a relationship between BMI and liver disease mortality in women.

After excluding all deaths occurring in the first five years of follow-up (which included 17 deaths from liver disease in men and 3 in women), the associations for men strengthened (table 3). Overweight men had a 52% higher rate of all liver disease mortality than under/normal weight men and obese men had more than a 4-fold higher rate. Risk factor adjustment had a small effect, with the relative rate for a SD increase in BMI remaining strong (1.47 (95% CI 1.25 to 1.73)). Again similar results were seen for the liver disease mortality subcategories, and no effect of BMI was seen on liver disease mortality in women.

With liver disease defined as any mention on the death certificate, SMR1 or cancer registration, there were 325 men (2.5%) and 155 women (1.7%) with liver disease (table 4). This analysis used 13 027 men and 9 328 women from the Collaborative and Renfrew/Paisley studies in 28 years of follow-up, when the proportional hazards assumption was satisfied. There were strong associations between BMI and liver disease in men (RR for 1 SD increase =1.22 (95% CI 1.09 to 1.36)), with 26% higher rates for overweight men and over double the rates for obese men, compared to the under/normal weight men. Adjustment for risk factors again had a small effect on the relative rates. There was a suggestion of a relationship between BMI and liver disease in women, although confidence intervals included one. Unlike the mortality analysis where only one cause was possible, the definition of “having liver disease” meant that a participant could be included in both the subcategories giving rise to larger numbers of cases in the two subcategories than for all liver disease in table 4. For example, a participant with liver cancer could also have cirrhosis of the liver. Obese men had more than twice the rate of liver cancer than under/normal weight men, but there was little evidence of a dose-response relationship. BMI was strongly related to all other causes of liver disease and these relationships remained after adjustment for risk factors. There was some evidence of an association between BMI and liver disease in women, in particular for the fully adjusted liver cancer model and for all other liver disease adjusted for age and study, where one SD increase in BMI was associated with an 18% increased relative rate.

Excluding the underweight from the analyses gave very similar results (tables available on web).

## Discussion

In this prospective cohort study, BMI was strongly associated with an increased risk of mortality from liver disease in men, with overweight and obese men having a 52% and a 4-fold higher rate respectively compared to other men. Relationships were also seen between BMI and men who had liver disease (defined from any of the available sources), with a suggestion of an association for women. The ability to define liver disease in this way is important, since some participants may have died of another cause (such as coronary heart disease) and so would not appear as cases in the mortality analyses. BMI was also associated with the subcategories of liver disease, cancer and all other liver disease, with the relationship being stronger for all other liver disease than for liver cancer. The Prospective

Studies Collaboration found evidence of a positive relationship between BMI and liver disease mortality, subdivided into cancer or non-cancer during a short follow-up period20. This was mainly seen in the upper range of BMI (25-50 kg/m$^2$). Overall our findings for men were similar to those seen in the Whitehall study of male civil servants10. Findings for liver cancer mortality were somewhat stronger in the Midspan studies, with narrower confidence intervals. The similarities between the two studies provide more evidence of the link between obesity and liver disease mortality. We have extended the previous findings to show that the BMI-liver disease relationship is present in general and working populations and that it is apparent when non-fatal liver disease is included in the outcomes. We were able to investigate BMI and liver disease in women and found little evidence of a relationship in these cohorts. This could be due to the smaller numbers of women and would need to be investigated in larger studies before dismissing any such relationships in women.

An association between BMI and various liver diseases has been observed in several previous studies, although the pathophysiological mechanisms that link them remain unclear21. Non alcoholic fatty liver disease is the most common form of adult liver disease in the USA22 and may be regarded as the “hepatic manifestation of the metabolic syndrome”23 as insulin resistance is an important factor in its development24. Insulin resistance leads to accumulation of fat within hepatocytes as a result of both hyperinsulinaemia and lipolysis. Obesity was found to be associated with cirrhosis-related death or hospitalisation in the United States NHANES study9 –a prospective cohort study like the current study. Hepatic steatosis was found in 1 in 3 adults in a general population sample in the United States25. Williams consequently noted that the high numbers of overweight or obese Americans could be the basis of a new epidemic of cirrhosis26. Evidence has been accumulating on the association of BMI with liver cancer, and a meta-analysis showed relative risks of 1.17 (95% CI 1.02 to 1.34) for liver cancer in overweight and 1.89 (95% CI 1.51 to 2.36) in obese compared to normal weight people, with stronger effects in men than women8. In the current study’s analysis of having liver cancer, we found similar relative rates for men. However, the effect of BMI on liver cancer risk is less clear in women than men27. Relative risks of liver cancer mortality in the highest compared with the lowest BMIs have been reported as 1.68 (95% CI 0.93 to 3.05) in women and 4.52 (95% CI 2.94 to 6.94) in men28.

## Strengths and limitations of the study

The study was large with over 26,000 participants and had a long follow-up period of up to 42 years. BMI was measured at screening, as opposed to cross-sectional or clinical studies where it is not possible to determine whether BMI was the cause of liver disease or was caused by it. The study also benefited by the availability of the linked Scottish hospital data which is currently unavailable in the rest of the UK. The inclusion of women in studies of this era was an added advantage. Having large numbers of participants meant the effect of excluding deaths in the first 5 years of follow-up, when pre-existing disease may cause BMI to be lower than usual, could be investigated. As predicted, these analyses found stronger relationships than in the whole follow-up period, suggesting associations of BMI with liver disease mortality in the whole follow-up period were underestimates. Limitations were that BMI was measured at screening and could have changed in the follow-up period. This is a disadvantage of prospective cohort studies which can only be overcome by multiple resurveys over the whole follow-up period. Hospital discharge data and cancer registrations were not available in the Main study. However, the numbers available with those data were still large at over 22 000. Although weight and height were self-reported in the Main study, evidence from another study of adults in Scotland showed this was unlikely to underestimate the actual BMI29. Unlike in other populations, where height is usually over-reported and weight under-reported30, that study showed both height and weight to be under-reported,

resulting in a negligible effect on BMI29. Alcohol consumption is well-known to be associated with liver disease, but since alcohol consumption was not measured in the Renfrew/Paisley study, alcohol could not be included in this study. However another analysis using men from the Main and Collaborative studies, who answered a question on weekly alcohol consumption, has examined both BMI and alcohol in relation to liver disease. Waist and hip measurements were not taken in the studies, so alternative measures of obesity, such as the waist/hip ratio or the just the waist measurement, could not be used. Future investigations using other studies which have these variables would be welcomed.

## Generalisability

As the participants were from general and working populations, the results should be generalisable to other populations. Levels of obesity have increased since the Midspan studies were carried out, and in 2003 Scotland had among the highest levels of obesity in the OECD countries, second only to the United States31. However, there was little difference in obesity levels between Scotland and England, with a 3.5% higher prevalence in women and a negligible difference in men31. It would be expected that the BMI-liver disease relationship found in this paper would be seen in other countries where overweight and obesity levels are high.

To conclude, we have contributed to the evidence that obesity is related to liver disease. This should aid health service planning of specialist services for liver disease, help primary care in better identifying, quantifying and managing the risk of liver disease associated with overweight and obesity, and improve public awareness of the links between BMI and liver disease. With obesity at unprecedented levels, and predicted to increase further, will the next chronic disease epidemic be of liver disease?

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Table 1

Age adjusted risk factors, means or percentages with 95% confidence intervals, in the Main, Collaborative and Renfrew/Paisley studies combined

| | BMI category | | |
|---|---|---|---|
| | **Under /Normal weight** | **Overweight** | **Obese** |
| **Men** | | | |
| Number of men | 7858 | 7389 | 1275 |
| Main | 2037 | 1291 | 167 |
| Collaborative | 2967 | 2690 | 359 |
| Renfrew/Paisley | 2854 | 3408 | 749 |
| *Means* | | | |
| Age (years) | 49.2 (49.0 to 49.5) | 50.9 (50.7 to 51.1) | 52.1 (51.7 to 52.5) |
| Systolic blood pressure (mmHg) | 137.3 (136.9 to 137.8) | 142.7 (142.2 to 143.2) | 150.8 (149.5 to 152.0) |
| FEV1 (L) | 273.0 (271.4 to 274.6) | 280.9 (279.3 to 282.5) | 271.8 (268.0 to 275.5) |
| *%s* | | | |
| Never smoker | 13.6 (12.8 to 14.3) | 19.0 (18.1 to 19.9) | 24.2 (21.7 to 26.6) |
| Current smoker | 68.7 (67.7 to 69.7) | 53.6 (52.4 to 54.7) | 47.8 (45.0 to 50.6) |
| Ex-smoker | 17.7 (16.8 to 18.5) | 27.5 (26.4 to 28.5) | 28.0 (25.6 to 30.5) |
| Diabetic | 0.9 (0.6 to 1.1) | 0.8 (0.6 to 1.0) | 1.4 (0.8 to 2.1) |
| Angina | 7.1 (6.5 to 7.7) | 7.6 (7.0 to 8.2) | 8.7 (7.2 to 10.3) |
| MRC bronchitis | 4.1 (3.7 to 4.6) | 3.7 (3.3 to 4.1) | 4.1 (3.1 to 5.2) |
| ECG ischaemia | 6.2 (5.7 to 6.7) | 9.0 (8.3 to 9.6) | 11.7 (10.0 to 13.4) |
| Manual social class | 63.2 (62.1 to 64.3) | 60.8 (59.7 to 61.9) | 68.4 (65.8 to 71.1) |
| **Women** | | | |
| Number of women | 5176 | 3635 | 1405 |
| Main | 582 | 232 | 74 |
| Collaborative | 581 | 342 | 78 |
| Renfrew/Paisley | 4013 | 3061 | 1253 |
| *Means* | | | |
| Age (years) | 51.3 (51.0 to 51.5) | 53.6 (53.4 to 53.8) | 54.8 (54.4 to 55.1) |
| Systolic blood pressure (mmHg) | 142.7 (142.1 to 143.4) | 150.1 (149.9 to 150.9) | 161.1 (159.6 to 162.5) |
| FEV1 (L) | 179.8 (178.5 to 181.2) | 179.1 (177.5 to 180.7) | 173.3 (170.6 to 176.0) |
| *%s* | | | |
| Never smoker | 36.5 (35.2 to 37.8) | 52.0 (50.4 to 53.6) | 57.8 (55.1 to 60.5) |
| Current smoker | 56.6 (55.2 to 57.9) | 40.5 (38.9 to 42.1) | 35.2 (32.6 to 37.8) |
| Ex-smoker | 6.9 (6.2 to 7.6) | 7.5 (6.6 to 8.3) | 7.0 (5.6 to 8.4) |
| Diabetic | 0.8 (0.5 to 1.0) | 1.2 (0.8 to 1.5) | 2.0 (1.3 to 2.7) |
| Angina | 7.3 (6.6 to 8.1) | 9.4 (8.4 to 10.3) | 14.4 (12.5 to 16.2) |
| MRC bronchitis | 3.7 (3.2 to 4.2) | 3.5 (2.9 to 4.1) | 5.1 (4.0 to 6.3) |
| ECG ischaemia | 7.8 (7.1 to 8.6) | 10.1 (9.1 to 11.1) | 13.3 (11.5 to 15.0) |
| Manual social class | 53.6 (52.2 to 55.0) | 60.6 (59.0 to 62.2) | 67.5 (64.9 to 70.1) |

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**Table 2**

Relative rates of liver disease mortality in relation to body mass index in the Main, Collaborative and Renfrew/Paisley studies combined

| | BMI category | | | p | 1SD increase in BMI |
|---|---|---|---|---|---|
| | Under/ Normal weight | Overweight | Obese | | |
| **Men** | | | | | |
| Number of men | 7858 | 7389 | 1275 | | |
| **All liver disease** | | | | | |
| Number of deaths | 53 | 67 | 26 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.34 (0.93 to 1.93) | 3.46 (2.14 to 5.59) | <0.0001 | 1.41 (1.21 to 1.65) |
| Relative rate$_2$ (95% CI) | 1 | 1.37 (0.95 to 1.98) | 3.30 (2.01 to 5.41) | <0.0001 | 1.38 (1.18 to 1.62) |
| **Liver cancer** | | | | | |
| Number of deaths | 20 | 20 | 9 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.0 (0.54 to 1.88) | 3.03 (1.36 to 6.78) | 0.034 | 1.35 (1.02 to 1.78) |
| Relative rate$_2$ (95% CI) | 1 | 1.01 (0.54 to 1.91) | 3.05 (1.33 to 7.0) | 0.039 | 1.35 (1.01 to 1.79) |
| **All other liver disease** | | | | | |
| Number of deaths | 33 | 47 | 17 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.56 (0.99 to 2.45) | 3.73 (2.05 to 6.78) | <0.0001 | 1.45 (1.20 to 1.74) |
| Relative rate$_2$ (95% CI) | 1 | 1.58 (1.0 to 2.49) | 3.42 (1.85 to 6.33) | <0.0001 | 1.39 (1.16 to 1.68) |
| **Women** | | | | | |
| Number of women | 5176 | 3635 | 1405 | | |
| **All liver disease** | | | | | |
| Number of deaths | 27 | 26 | 8 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.35 (0.78 to 2.33) | 1.25 (0.57 to 2.78) | 0.52 | 1.09 (0.84 to 1.42) |
| Relative rate$_2$ (95% CI) | 1 | 1.38 (0.80 to 2.41) | 1.21 (0.53 to 2.78) | 0.59 | 1.08 (0.82 to 1.42) |
| **Liver cancer** | | | | | |

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| | BMI category | | | p | 1SD increase in BMI |
|---|---|---|---|---|---|
| | Under/ Normal weight | Overweight | Obese | | |
| Number of deaths | 11 | 7 | 2 | | |
| Relative rate$_1$ (95% CI) | 1 | 0.84 (0.32 to 2.18) | 0.76 (0.17 to 3.46) | 0.95 | 0.98 (0.60 to 1.61) |
| Relative rate$_2$ (95% CI) | 1 | 1.06 (0.40 to 2.80) | 1.11 (0.24 to 5.27) | 0.52 | 1.18 (0.71 to 1.95) |
| **All other liver disease** | | | | | |
| Number of deaths | 16 | 19 | 6 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.73 (0.88 to 3.38) | 1.61 (0.62 to 4.16) | 0.40 | 1.14 (0.84 to 1.55) |
| Relative rate$_2$ (95% CI) | 1 | 1.63 (0.82 to 3.24) | 1.27 (0.47 to 3.46) | 0.86 | 1.03 (0.74 to 1.43) |

Relative rate $_1$ adjusted for age and study

Relative rate $_2$ adjusted for age, study, social class, smoking, systolic blood pressure, height, ischaemia on ECG, bronchitis, FEV1, angina and diabetes

CI confidence interval

SD standard deviation

1 SD=3.25kg/m$^2$ for men, 4.39 kg/m$^2$ for women

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**Table 3**

Relative rates of liver disease mortality in relation to body mass index in the Main, Collaborative and Renfrew/Paisley studies combined, excluding deaths in 1st 5 years

| | BMI category | | | p | 1SD increase in BMI |
|---|---|---|---|---|---|
| | Under/ Normal weight | Overweight | Obese | | |
| **Men** | | | | | |
| Number of men | 7371 | 6931 | 1165 | | |
| **All liver disease** | | | | | |
| Number of deaths | 44 | 61 | 24 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.52 (1.03 to 2.25) | 4.14 (2.48 to 6.88) | <0.0001 | 1.53 (1.30 to 1.79) |
| Relative rate$_2$ (95% CI) | 1 | 1.53 (1.03 to 2.28) | 3.81 (2.25 to 6.44) | <0.0001 | 1.47 (1.25 to 1.73) |
| **Liver cancer** | | | | | |
| Number of deaths | 17 | 18 | 9 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.08 (0.55 to 2.11) | 3.75 (1.64 to 8.59) | 0.008 | 1.47 (1.10 to 1.95) |
| Relative rate$_2$ (95% CI) | 1 | 1.10 (0.56 to 2.17) | 3.80 (1.61 to 8.97) | 0.011 | 1.47 (1.09 to 1.97) |
| **All other liver disease** | | | | | |
| Number of deaths | 27 | 43 | 15 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.81 (1.11 to 2.95) | 4.38 (2.30 to 8.37) | <0.0001 | 1.56 (1.28 to 1.89) |
| Relative rate$_2$ (95% CI) | 1 | 1.80 (1.10 to 2.95) | 3.79 (1.95 to 7.37) | <0.0001 | 1.47 (1.21 to 1.78) |
| **Women** | | | | | |
| Number of women | 4962 | 3490 | 1331 | | |
| **All liver disease** | | | | | |
| Number of deaths | 27 | 24 | 7 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.25 (0.72 to 2.18) | 1.11 (0.48 to 2.58) | 0.77 | 1.04 (0.79 to 1.37) |
| Relative rate$_2$ (95% CI) | 1 | 1.27 (0.72 to 2.24) | 1.07 (0.45 to 2.57) | 0.85 | 1.03 (0.77 to 1.37) |

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| | BMI category | | | p | 1SD increase in BMI |
|---|---|---|---|---|---|
| | Under/ Normal weight | Overweight | Obese | | |
| **Liver cancer** | | | | | |
| Number of deaths | 11 | 7 | 2 | | |
| Relative rate$_1$ (95% CI) | 1 | 0.84 (0.32 to 2.18) | 0.76 (0.17 to 3.46) | 0.95 | 0.98 (0.60 to 1.61) |
| Relative rate$_2$ (95% CI) | 1 | 1.06 (0.40 to 2.80) | 1.11 (0.24 to 5.27) | 0.52 | 1.18 (0.71 to 1.95) |
| **All other liver disease** | | | | | |
| Number of deaths | 16 | 17 | 5 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.56 (0.78 to 3.11) | 1.37 (0.50 to 3.79) | 0.68 | 1.07 (0.77 to 1.50) |
| Relative rate$_2$ (95% CI) | 1 | 1.44 (0.71 to 2.92) | 1.06 (0.36 to 3.08) | 0.80 | 0.96 (0.67 to 1.36) |

Relative rate 1 adjusted for age and study

Relative rate 2 adjusted for age, study, social class, smoking, systolic blood pressure, height, ischaemia on ECG, bronchitis, FEV1, angina and diabetes

CI confidence interval

SD standard deviation

1 SD=3.25kg/m$^2$ for men, 4.39 kg/m$^2$ for women

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**Table 4**

Liver ascertained by any position on death certificate, any position on SMR1 or cancer registration for the Collaborative and Renfrew/Paisley studies combined, limited to 28 years of follow up

| | BMI category | | | p | 1SD increase in BMI |
|---|---|---|---|---|---|
| | Under/ Normal weight | Overweight | Obese | | |
| **Men** | | | | | |
| Number of men | 5821 | 6098 | 1108 | | |
| **All liver disease** | | | | | |
| Number with liver disease | 118 | 161 | 46 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.26 (1.0 to 1.60) | 2.14 (1.52 to 3.01) | <0.0001 | 1.22 (1.09 to 1.36) |
| Relative rate$_2$ (95% CI) | 1 | 1.28 (1.0 to 1.63) | 1.96 (1.37 to 2.80) | 0.002 | 1.19 (1.06 to 1.32) |
| **Liver cancer** | | | | | |
| Number with liver cancer | 26 | 30 | 11 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.05 (0.62 to 1.77) | 2.27 (1.11 to 4.62) | 0.19 | 1.17 (0.92 to 1.49) |
| Relative rate$_2$ (95% CI) | 1 | 1.17 (0.68 to 2.0) | 2.53 (1.22 to 5.28) | 0.09 | 1.23 (0.97 to 1.57) |
| **All other liver disease** | | | | | |
| Number with all other liver disease | 98 | 136 | 42 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.30 (1.0 to 1.68) | 2.39 (1.66 to 3.44) | <0.0001 | 1.26 (1.12 to 1.41) |
| Relative rate$_2$ (95% CI) | 1 | 1.29 (0.99 to 1.68) | 2.09 (1.43 to 3.05) | 0.002 | 1.20 (1.07 to 1.35) |
| **Women** | | | | | |
| Number of women | 4594 | 3403 | 1331 | | |
| **All liver disease** | | | | | |
| Number with liver disease | 68 | 61 | 26 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.22 (0.86 to 1.73) | 1.47 (0.93 to 2.32) | 0.08 | 1.15 (0.98 to 1.34) |

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| | BMI category | | | p | 1SD increase in BMI |
|---|---|---|---|---|---|
| | Under/ Normal weight | Overweight | Obese | | |
| Relative rate$_2$ (95% CI) | 1 | 1.24 (0.87 to 1.77) | 1.37 (0.85 to 2.21) | 0.15 | 1.13 (0.96 to 1.32) |
| **Liver cancer** | | | | | |
| Number with liver cancer | 15 | 8 | 5 | | |
| Relative rate$_1$ (95% CI) | 1 | 0.71 (0.30 to 1.69) | 1.33 (0.48 to 3.69) | 0.09 | 1.33 (0.96 to 1.86) |
| Relative rate$_2$ (95% CI) | 1 | 0.84 (0.35 to 2.02) | 1.47 (0.50 to 4.31) | 0.038 | 1.39 (1.02 to 1.91) |
| **All other liver disease** | | | | | |
| Number with all other liver disease | 57 | 53 | 25 | | |
| Relative rate$_1$ (95% CI) | 1 | 1.27 (0.87 to 1.84) | 1.68 (1.05 to 2.70) | 0.04 | 1.18 (1.01 to 1.39) |
| Relative rate$_2$ (95% CI) | 1 | 1.27 (0.87 to 1.86) | 1.53 (0.93 to 2.52) | 0.11 | 1.15 (0.97 to 1.36) |

Relative rate$_1$ adjusted for age and study

Relative rate$_2$ adjusted for age, study, social class, smoking, systolic blood pressure, height, ischaemia on ECG, bronchitis, FEV1, angina, diabetes and cholesterol.

CI confidence interval

SD standard deviation

1 SD=3.27kg/m$^2$ for men, 4.42 kg/m$^2$ for women