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**Abnormal liver tests in people aged 75 and over: prevalence  
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## Abnormal liver tests in people aged 75 and over: prevalence and association with mortality.

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41 Running title: Abnormal liver tests in the elderly

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Keywords: liver tests, liver function tests, mortality, prevalence

## Abstract

**Background:** Despite their common use the occurrence and consequences of abnormal liver tests are unclear.

**Aims:** To estimate the prevalence and mortality associated with abnormal liver tests in people aged 75 years and over.

**Methods:** A cohort study on 13276 people aged 75 years and over, registered with general practices, with a valid measurement of one or more liver test, calculating the prevalence of abnormal aspartate transaminase (AST), alkaline phosphatase (ALP) or bilirubin. Hazard ratios (HRs) were calculated for all-cause and cause-specific mortality comparing elderly patients with abnormal liver tests to elderly patients with normal liver tests.

**Results** At least one abnormal liver test was found in 2175 subjects (16.1%, 95% CI [15.4%, 16.7%]). The prevalence of a single abnormal liver test was 3.3% (95% CI [3.0%, 3.7%]) for AST, 9.2% (95% CI [8.8%, 9.7%]) for ALP and 5.4% (95% CI [5.1%, 5.9%]) for bilirubin. Abnormal AST, ALP and bilirubin were associated with increased risks of all cause mortality; adjusted HRs 1.27 (95% CI [1.09, 1.47]), 1.47 (95% CI [1.35, 1.61]) and 1.15 (95% CI [1.02, 1.30]) respectively. Abnormal AST and ALP were associated with a 7- and 6-fold increased risk of death from liver disease respectively. Two or more abnormal liver tests were associated with 2-fold and 17-fold increased risk of death from cancer and liver disease respectively. Of the causes examined, absolute mortality rates were highest for cardiovascular disease in subjects with and without abnormal liver tests.

**Conclusions** Abnormal liver tests occur commonly in elderly people and are associated with a modest increase in all-cause mortality. There was a strong association with liver disease however the majority of deaths were not due to this cause.

## Introduction

In the UK liver biochemistry tests are frequently performed both in primary and secondary care and are often termed “liver function tests” frequently including measurements of serum aminotransferase, alkaline phosphatase and bilirubin. A finding of an elevation of one or more of these tests may be used as an indication of potential liver disease with subsequent follow-up and more invasive testing probable. Despite their common use what the occurrence and consequences of these abnormalities are remains unclear.

Older people represent an increasingly large group of health-care users in the UK. An estimated 40% of all 75-79 year olds have at least one prescription for statins per year[1] and liver tests are performed in this group often to determine their suitability for prescription of statins.[2] Many of the misconceptions regarding statins have since been challenged; idiosyncratic hepatotoxicity from statins is rare and prior liver test abnormalities are not now considered a contraindication to statin prescription.[3] A recent study suggested that majority of liver test abnormalities detected prior to statin prescription were due to non-alcoholic fatty liver disease and relative risk reduction in cardiovascular events from statins was greater in patients with prior liver test abnormalities compared with those with normal liver tests.[4] However, liver tests are still routinely performed, and it is surprising that we do not have any robust information on the proportion of older people with elevated liver tests or what any abnormalities in these tests may mean for their future health. Currently primary care physicians and hepatologists use a pragmatic approach to the management of these abnormalities, in the absence of evidence to the contrary, whereby repeated measurements are made before further investigation is carried out.

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3 To date only four population based studies in The Netherlands[5], South Korea[6] the  
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5 USA[7] and Scotland[8] have examined the relationship between liver tests and all-  
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7 cause mortality in adults with conflicting conclusions as to the magnitude of any  
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9 association primarily due to the wide variation in populations studied and, with  
10  
11 respect to the European studies, no truly population based approach. No studies  
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13 have particularly concentrated on a population of older people.  
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18 We therefore aimed to estimate the prevalence of abnormal liver tests in a random  
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20 sample of people aged 75 and over; to examine the association between abnormal  
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22 liver tests and demographic, lifestyle and clinical characteristics in people aged 75  
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24 and over; and to determine the risk of all cause and cause-specific mortality in elderly  
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26 people with abnormal liver tests.  
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## Methods

### Data source and participants

We used data collected as part of the Medical Research Council (MRC) Trial of Assessment and Management of Older People in the Community. Full details of the trial protocol and results have been reported[9], [10]. Briefly, 106 practices were recruited through the MRC General Practice Research Framework, selected to represent the population of the UK based on mortality (Standardised Mortality Ratios) and deprivation[11]. All people aged 75 or over registered with these selected general practices, non-resident in nursing homes, and who were not known to be terminally ill, were eligible for this trial which comprised two arms comparing multi-dimensional assessment of the elderly. One arm (universal arm) invited all patients to an in-depth health assessment whilst the other arm (targeted arm) invited only selected patients. We used data only from participants in the universal arm (53 practices) as they were considered a representative sample of community dwelling older people. A total of 15 308 of 20 934 (73.1%) potential participants attended for baseline assessment in the universal arm. Nonresponders were more likely to be women and were older.[12] Data collection took place between 1995 and 1999. Local Research Ethics Committee approvals were obtained for each participating practice.

### Data collection and definitions

Socio-demographic information, self-reported medical history and lifestyle data (including alcohol consumption and smoking history) were obtained at the in depth assessment by nurse interviews. Body Mass Index (BMI) was defined as weight (in kg) divided by height (in m) squared, each of which were measured once. Waist circumference was measured to the nearest 0.1cm midway between the iliac crest and the lower rib margin by using an insertion tape. Hip circumference was

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3 measured as the widest circumference over the buttocks and below the iliac crest.  
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5 Hip and waist were both measured twice (having asked patients to roll down their  
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7 undergarments) and an average of the two values used in the calculation of waist:hip  
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9 ratio (WHR). Diabetes was classified as present following either a self-reported  
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11 medical diagnosis, prescription of anti-diabetic medication or a single high random  
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13 blood glucose measurement. Heart attack, hypertension, stroke, cancer and ulcer  
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15 were defined as a positive self-reported medical diagnosis. We used the Rose Chest  
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17 Pain questionnaire[13] and categorised definite angina as chest pain that limits  
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19 exertion, is situated over the sternum or in the left chest and left arm, and is relieved  
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21 within 10 minutes by rest. Severe dementia was defined as a score of <9 /30 on the  
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23 Mini-Mental State examination[14]. In order to assess the impact of multiple  
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25 illnesses a co-morbidity score was derived. A patient was given a score of zero (not  
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27 present) or one (present ever before the date of interview) for each of the following  
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29 self-reported medical conditions: asthma, stomach / digestive ulcer, hypertension,  
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31 heart attack, stroke, fractured hip or spine (within last year only), Parkinson's  
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33 disease, cancer, and for each of the following: angina, dementia and diabetes (as per  
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35 definitions above). Scores were added together to give an overall score and then  
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37 categorised into 0, 1, 2 and 3 or more comorbidities.  
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45 At the assessment participants provided a blood sample which was sent to the local  
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47 laboratory for a standard blood examination including aspartate transaminase (AST),  
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49 alkaline phosphatase (ALP) and bilirubin (which we will henceforth collectively refer  
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51 to as liver tests). In order to determine whether a patient had an abnormal liver test  
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53 we requested reference ranges from the laboratories that provided the testing  
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55 services for the practices involved in this arm of the trial. Reference ranges were not  
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57 collected at the time of the study and only half of the practices involved had any  
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59 recorded reference ranges for the three liver tests of interest. For those practices  
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(n=25) where we did not have a provided reference range a median reference range



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3 was imputed. Abnormal liver tests were determined as the result being above the  
4 upper limit of normal relative to the reported or imputed laboratory reference range.  
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7 Abnormal results were then categorised as being between 1 and 2x the upper limit of  
8 normal or above 2x the upper limit of normal.  
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14 All participants in the trial were registered with the NHS central register for mortality  
15 follow-up and coded cause of death, date of death or date of migration for all  
16 individuals were provided through the UK Office for National Statistics. Deaths were  
17 coded according to the International Classification for Diseases, 9<sup>th</sup> revision (ICD9)  
18 until September 2002, and according to the 10<sup>th</sup> revision (ICD10) afterwards.  
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21 Specifically examined causes of death were cardiovascular disease (ICD9 401-405,  
22 410-414, 425-447; ICD10 I10-I15, I20-I25, I42-I52, I6-I77, I79), cancer (all cancers  
23 excluding liver cancer (ICD9 140-154, 156-239; ICD10 C0-C21, C23-D4)), respiratory  
24 disease (ICD9 46-51; ICD10 J) and liver disease (viral hepatitis, liver cancer and liver  
25 disease (ICD9 070, 155, 570-573; ICD10 B15-B19, C22, K7)).  
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### 38 **Statistical analyses**

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40 Prevalences of abnormal liver tests were calculated as the number of people with an  
41 abnormal result divided by the number of subjects with a valid test or combination of  
42 tests. 95% CIs were calculated using the binomial distribution.  
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46 To examine the association between abnormal liver tests and demographic, lifestyle  
47 and medical characteristics we used logistic regression to calculate odds ratios and  
48 95% CIs, with standard errors adjusted to account for potential clustering within  
49 practices. Alcohol consumption was categorised in groups of 7-unit increments. BMI  
50 was categorised using accepted definitions[15] and WHR was categorised in 0.1 unit  
51 bands. After univariate analyses, a priori confounders of age, sex and comorbidity  
52 plus additional statistically significant associations were built into a multivariate  
53 logistic regression model to account for potential confounding.  
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6 In the mortality analysis subjects were considered as contributing time to the analysis  
7 from the date of interview until death, censoring (migration) or 5 November 2005 (the  
8 last date of available data from the ONS) whichever came earliest. All cause and  
9  
10 cause-specific mortality were examined for each abnormal liver test in turn.

11  
12 Associations between death and demographic, lifestyle and medical characteristics  
13 were examined in a control population consisting of all those elderly people without  
14 any liver test abnormality in order to identify appropriate confounding variables. Cox  
15  
16 proportional hazards regression analysis was used to compare the survival of elderly  
17  
18 people with normal liver tests to elderly people with abnormal liver tests. A priori  
19  
20 confounders of age, sex and co-morbidity, as well as other identified confounders for  
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22 individual liver tests, were included within multivariate cox proportional hazards  
23  
24 models to provide adjusted hazard ratios. Proportional hazards assumptions were  
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26 checked using Schoenfeld residuals and log-log plots.  
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35 All data management and analyses were conducted using Stata software [version  
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37 9.2SE]  
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## Results

### Prevalence of abnormal liver tests

Of 15 308 participants aged 75 and over in the universal arm of the trial, 13 276 (86.7%) had at least one valid measurement of a liver test. Participants who did not have a valid test result were more likely to be female, were slightly older and had a slightly greater co-morbidity index. Participants without valid measurements were also more likely to have missing data for other variables examined.

Overall, 16.1% of those with one or more valid measurement had at least one abnormal liver test. The most common abnormal liver test within this population was ALP with 9.2% (95%CI [8.7%, 9.7%]) of people having a result above the upper limit of normal (Table 1). Only 5.4% (95%CI [5.0%, 5.8%]) of people had an abnormal bilirubin test, whilst an even smaller proportion had an abnormal AST result, 3.3% (95%CI [3.0%, 3.7%]) of those with a valid measurement. The majority of subjects with an abnormal measurement had a test result less than or equal to 2x the upper limit of normal: 86.2% AST; 90.0% ALP, 93.8% bilirubin.

### Demographic, lifestyle and medical characteristics associated with an abnormal liver test

Having an abnormal AST measurement was associated with a lower age and with alcohol consumption of 7 units or more in the previous week. (Table 2) Conversely, people with an elevated ALP measurement were more likely to be older and to have a lower alcohol consumption. A history of diabetes and an assessment of dementia were associated with both elevated AST and ALP, with a history of heart attack associated only with increased ALP. Categorisation of comorbidity score showed an association only with abnormal ALP. An abnormal bilirubin was strongly associated with male sex and being a current or ex-smoker appeared to confer a protective effect on having an abnormal bilirubin following adjustment for other variables.

**Mortality associated with abnormal liver tests.****AST**

The median follow-up for mortality was 7.2 years (80,071 person-years of follow-up) with 7590 deaths. Mortality in subjects with an abnormal AST was 104.8 per 1000 person-years representing an increase of 10 deaths per 1000 person-years of follow-up compared to subjects with a normal AST (Table 3). This corresponded to an adjusted hazard ratio of 1.27, i.e. an abnormal AST was associated with a 27% (95% CI [9%, 47%]) increased hazard for all-cause mortality. There was an increased hazard of death with increasing levels of abnormality with patients with an abnormal AST over 2x the ULN having a 62% increased hazard of death. Abnormal AST was associated with increase in mortality from cancer (56% increased hazard) and mortality from liver disease (7-fold increased hazard) (Table 3). It should be noted that only 8 out of 429 subjects (1.8%) with an abnormal AST died from liver disease.

**ALP**

The median follow-up for mortality was 7.2 years (84,256 person-years of follow-up) with 7971 deaths. Mortality in subjects with an abnormal ALP was 138.8 per 1000 person-years of follow-up representing an increase of nearly 50 deaths per 1000 person years compared with subjects with a normal ALP measurement (Table 4). An abnormal ALP measurement was associated with a 47% increase in hazard of death, adjusted for age, sex, co-morbidity score and alcohol intake (hazard ratio 1.47; 95% CI [1.35, 1.61]). An abnormal ALP was associated with an increased hazard for death from CVD (34% increase), death from cancer (61% increase), death from respiratory disease (58% increase) and death from liver disease (nearly 6-fold increase) (Table 4). However, only 13 out of 1246 subjects (1.0%) with an abnormal ALP died from liver disease.

### **Bilirubin**

The median follow-up for mortality was 7.2 years (79,285 person-years of follow-up) with 7479 deaths. Abnormal bilirubin was associated with a small increase in hazard of death (15%, 95%CI [2%, 30%]) following adjustment for the confounding factors of age, sex, comorbidity score, smoking status, alcohol intake and WHR group (Table 5). Abnormal bilirubin was not associated with a change in hazard of any cause-specific mortality examined (Table 5).

### **Multiple elevations of liver tests**

181 subjects had two or more elevated liver tests. Having two or more elevated liver tests was associated with an increased hazard of all-cause mortality (adjusted HR 1.54 (95%CI [1.30, 1.83])), a doubling in hazard of death from cancer and a 14-fold increase in hazard of death from liver disease compared to subjects with no abnormal liver tests (Table 6).

## Discussion

We found that nearly 1 in 6 of the general population aged 75 and over had at least one elevated liver test of AST, ALP or bilirubin. Over half of these abnormalities can be accounted for by an elevated measurement of ALP (9.2% of all subjects) and the vast majority were within 1 x the ULN for the test measured. A single abnormal liver test in this elderly population was associated with a higher risk of death overall, and for AST and ALP in particular a higher risk of death from liver disease, compared to those elderly subjects with normal liver tests. The occurrence of two or more abnormal liver tests was associated with a 2-fold risk of death from cancer and a 14-fold risk of death from liver disease. The highest absolute mortality rates were seen for cardiovascular disease both in subjects with and without abnormal liver tests.

Although frequently performed as part of standard laboratory blood tests and bracketed under the nomenclature of 'liver functions tests', individual elevations of AST, ALP or bilirubin arguably do not reflect impaired liver function with AST also being found in skeletal muscle and the heart and ALP being particularly concentrated also in bones and the kidneys. Elevations of these enzymes would be considered indicative of liver injury or impairment if found in combination with elevations in other liver tests which might be considered more specific to the liver such as alanine aminotransferase (ALT) or gamma-glutamyl transpeptidase (GGT). Unfortunately, neither ALT nor GGT measurements were collected as part of the panel of blood tests in the original study from which these data are taken. We do not therefore know whether there were concurrent abnormalities in either ALT or GGT in those patients with elevated AST, ALP or bilirubin.

In addition to an unsurprising increased risk of death from liver disease (albeit mediated through very small absolute numbers of deaths) both elevated AST and

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3 ALP were seen to be associated with an increased risk of death from cancer  
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5 (excluding liver cancer). Elevated ALP was also associated with an increased risk of  
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7 death from cardiovascular and respiratory disease with absolute excess mortality for  
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9 both these causes being much greater than that observed for liver disease. Rather  
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11 than being related to liver function per se this may reflect the fact that these enzymes  
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13 are also present in the other body tissues referred to above and not just specific to  
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15 the liver. Indeed the associations seen between these "liver function tests" and the  
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17 presence of other non-liver diseases (diabetes, heart attack and dementia) support  
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19 this. When we considered subjects with more than one elevated liver test a greater  
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21 increased hazard of death from all causes and from cancer (adjusted HR 2.11 [1.59,  
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23 2.80]and liver disease [adjusted HR 17.0 [7.2, 40.2] respectively) was seen  
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25 compared to that seen in patients with only one isolated elevated liver test. We have  
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27 provided hazard ratios for death adjusted for self-reported comorbidity which may  
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29 only have measured significant comorbidity as determined by the participant. It is  
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31 possible that there may be other non-reported comorbidities associated with both  
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33 abnormal liver tests and mortality leading to some residual confounding in our study.  
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40 Our study relied on a single measurement of each of AST, ALP and bilirubin.  
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42 Naturally in the clinical setting it would be desirable to have multiple measurements  
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44 of these liver tests in order to assess whether a patient warranted further follow-up  
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46 and investigation. Our findings imply though that if the test result is not markedly  
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48 abnormal the absolute excess mortality following a single isolated abnormality for any  
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50 given individual is small with absolute excess mortality rates of 7.2, 10.3 and 47.9  
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52 deaths per 1000 person years in patients with abnormal bilirubin, AST and ALP  
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54 respectively.  
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60 As a result of the general practice design of this large study blood data were  
analysed across 48 laboratories. Unfortunately, not all laboratories were able to

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3 provide reference ranges for the liver tests so we relied on imputation for 25/53 of our  
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5 reference ranges. This means that we are unable to examine the association  
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7 between absolute values of enzymatic activity and mortality as many different  
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9 reference ranges were used.  
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13 Information on the prevalence and consequences of abnormal liver function in the UK  
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15 is surprisingly lacking. In this study we were able to assess, for the first time, some  
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17 commonly used markers of liver biochemical activity (even if they are not truly  
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19 specific for the liver) in a representative randomly selected community based sample  
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21 of people aged 75 and over. The representative nature of our study enables us to  
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23 provide a more accurate estimate of the prevalence of these abnormal liver tests in  
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25 the general population than has been previously available. Our results show a  
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27 slightly lower prevalence of abnormal transaminase (3.3% abnormal AST vs 7.0%  
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29 abnormal AST or alanine transaminase), ALP (9.2% vs 10.4%) and bilirubin (5.4% vs  
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31 7.1%) than those reported in the recent study of adults of all ages from Scotland[8].  
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33 This is expected as the population within this study was selected on the basis that  
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35 subjects already had a measurement of liver test contained within their primary care  
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37 records. The authors acknowledged that they did not know why liver tests were  
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39 requested and that this was likely to include the investigation of suspected liver  
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41 disease leading to a non-representative sample of the general population. In a study  
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43 in America[7], only a selected group of participants had blood tests, and it is likely  
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45 that the true population prevalence of abnormal liver tests may have been over  
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47 estimated. Indeed, 12.8% of those with a measurement of AST had an elevated  
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49 test, nearly four times that seen in our study. Other studies from the USA also show  
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51 a slightly higher prevalence of elevated AST to that which we have described in this  
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53 study, with 3.7% and 4.9% of the population aged 20 or over having an elevated AST  
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55 in 1988-1994 and 1999-2002 respectively[16],[17]. However, given that our study  
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57 looks only at people aged 75 and over, it may be that the prevalence of abnormal  
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3 liver tests in a population of older people is indeed lower than that found in the  
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5 general adult population of all ages.  
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10 Our data show an increased risk of death with a single measurement of abnormal  
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12 AST, consistent with those reported from America using the NHANES data[7] and  
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14 those in Scotland[8]. A higher risk of death was seen with increasingly abnormal  
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16 results in both these studies. Further studies from working populations in Germany  
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18 and South Korea report greater increases in all-cause mortality than those shown in  
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20 our data[18],[6].  
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25 We identified one study that specifically looked at the association between liver tests  
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27 and mortality in the elderly, which came from a small population of 70 year-olds in  
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29 Jerusalem[19]. This study did not show any significant associations between either  
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31 AST or ALP and all-cause mortality. However, the categorisation of the liver test  
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33 results as above or below the mean value in the study population makes the  
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35 interpretation of these results difficult to compare with our study where we were  
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37 specifically looking at abnormalities as defined by upper limits of normal reference  
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39 ranges.  
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44 Irrespective of the evidence, or lack of, to support the role of statins in hepatotoxicity,  
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46 current guidelines recommend liver tests should be carried out before and within 1-3  
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48 months of starting treatment on statins to monitor for signs of altered liver function[2].  
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50 With an estimated 40% of all 75-79 year olds having at least one prescription for  
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52 statins annually[1], incidental findings of elevated liver tests in this section of the  
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54 population in the absence of symptoms is likely to occur regularly. **Many referrals to  
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56 our hepatology clinics [GPA, JW] occur for investigation of abnormal “liver function  
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58 tests” in the elderly and there is little existing work to guide practitioners as to the  
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60 need for and the direction of further investigation. This is echoed by a report from**

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3 Department of Health Quality Strategy Team on Liver Disease which called for  
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5 guidance to be made available to general practitioners on the use and interpretation  
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7 of "liver function tests". However, to do this we need to understand the natural history  
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9 associated with the abnormalities found[20]. Our study has shown that abnormalities  
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11 in some liver enzymes are fairly common and they are associated with an increased  
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13 risk in all-cause mortality in the elderly population when compared with a similarly  
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15 elderly control population i.e. those subjects aged 75 and over with normal liver tests.  
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18 In the absence of any evidence for an overwhelming increase in mortality following a  
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20 single abnormal measurement of AST, ALP or bilirubin in isolation, it would seem  
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22 sensible that current practise of referral and active investigation of patients only with  
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24 multiple or persistent abnormalities should be continued.  
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Table 1. Prevalence of abnormal liver tests

Abnormal test(s) (Number with valid test)	Number abnormal (% of abnormal)	% of valid tests abnormal [95% CI]
<b>All 3 within reference range (N=11994)</b>	10025	83.6 [82.9, 84.2]
<b>Any abnormal (N=13546)</b>	2175	16.1 [15.4, 16.7]
<b>AST (N=12826)</b>	429 (100)	3.34 [3.04, 3.67]
≤ 2x upper range	370 (86.2)	2.88 [2.60, 3.19]
Above 2x upper range	59 (13.8)	0.46 [0.35, 0.59]
<b>ALP (N=13499)</b>	1246 (100)	9.23 [8.75, 9.73]
≤ 2x upper range	1122 (90.0)	8.31 [7.85, 8.79]
Above 2x upper range	124 (10.0)	0.92 [0.76, 1.09]
<b>Bilirubin (N=12690)</b>	690 (100)	5.44 [5.05, 5.85]
≤ 2x upper range	647 (93.8)	5.10 [4.72, 5.50]
Above 2x upper range	43 (6.2)	0.34 [0.25, 0.46]
AST and ALP (N=12794)	90	0.70 [0.57, 0.86]
AST and bilirubin (N=12021)	42	0.35 [0.25, 0.47]
ALP and bilirubin (N=12648)	67	0.52 [0.41, 0.67]
AST, ALP and bilirubin (N=11994)	9	0.07 [0.03, 0.14]

**Table 2 Associations between demographic characteristics and co-morbidities and abnormal liver tests**  
**All confidence intervals are calculated following adjustment for potential clustering in practices.**

	AST		ALP		Bilirubin	
	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
	Univariate	Multivariate*	Univariate	Multivariate**	Univariate	Multivariate***
<b>Sex</b>						
Female	0.96 [0.79, 1.18]	1.28 [0.94, 1.68]	1.05 [0.93, 1.19]	0.96 [0.83, 1.11]	0.37 [0.32, 0.44]	0.33 [0.26, 0.42]
Male	1	1	1	1	1	1
<b>Age</b>						
Yearly increase in age	0.97 [0.94, 0.99]	0.97 [0.94, 0.99]	1.05 [1.04, 1.07]	1.04 [1.03, 1.06]	0.99 [0.97, 1.01]	0.99 [0.97, 1.01]
<b>Alcohol</b>						
7unit increase in alcohol consumption in previous week	1.22 [1.08, 1.37]	1.16 [1.02, 1.32]	0.81 [0.74, 0.88]	0.83 [0.76, 0.91]	1.20 [1.09, 1.31]	1.06 [0.96, 1.17]
Drink in last year	0.84 [0.66, 1.08]		1.34 [1.17, 1.54]		0.85 [0.70, 1.04]	
<b>Smoking</b>						
Never	1		1		1	1
Ex	0.86 [0.70, 1.07]		0.82 [0.72, 0.94]		1.22 [1.03, 1.44]	0.79 [0.65, 0.97]
Current	0.97 [0.69, 1.35]		1.06 [0.86, 1.29]		1.76 [0.56, 1.05]	0.47 [0.32, 0.68]
<b>BMI</b>						
<18.5	0.73 [0.32, 1.69]		1.36 [0.93, 1.99]		0.95 [0.54, 1.66]	
18.5-	1		1		1	
25-	1.08 [0.86, 1.36]		0.85 [0.74, 0.98]		1.10 [0.92, 1.31]	
30-	1.26 [0.92, 1.72]		0.79 [0.64, 0.98]		0.91 [0.70, 1.19]	
35+	1.28 [0.72, 2.27]		1.52 [1.10, 2.10]		0.44 [0.22, 0.86]	
Missing						
Increase in BMI group	1.12 [0.99, 1.26]		0.95 [0.88, 1.03]		0.94 [0.85, 1.04]	
<b>Waist:hip ratio</b>						

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0.65-0.74	0.81 [0.42, 1.56]	0.66 [0.30, 1.45]	1.02 [0.72, 1.45]		1.36 [0.84, 2.20]	
0.75-0.84			-			
0.85-0.94	1.10 [0.86, 1.39]	1.14 [0.85, 1.52]	1.09 [0.94, 1.26]		1.73 [1.41, 2.12]	
0.95-1.04	1.12 [0.83, 1.51]	1.20 [0.81, 1.80]	0.99 [0.83, 1.21]		1.88 [1.48, 2.38]	
1.05-1.15	3.26 [1.88, 5.65]	3.73 [1.99, 6.99]	0.90 [0.53, 1.54]		1.65 [0.94, 2.90]	
Increase in WHR group	1.17 [1.03, 1.32]		1.01 [0.93, 1.08]		1.27 [1.15, 1.40]	0.90 [0.79, 1.03]
<b>Presence of comorbidity</b>						
Diabetes	1.53 [1.12, 2.10]		1.64 [1.35, 1.99]		1.12 [0.85, 1.48]	
Heart attack	0.87 [0.62, 1.22]		1.24 [1.03, 1.49]		0.97 [0.75, 1.25]	
Hypertension	1.13 [0.92, 1.39]		0.89 [0.78, 1.01]		1.00 [0.85, 1.18]	
Stroke	1.04 [0.73, 1.49]		1.05 [0.85, 1.29]		0.77 [0.57, 1.04]	
Cancer	1.09 [0.79, 1.50]		0.97 [0.80, 1.19]		0.90 [0.68, 1.17]	
Ulcer	1.15 [0.86, 1.54]		1.11 [0.92, 1.32]		1.14 [0.90, 1.43]	
Angina	0.88 [0.57, 1.36]		1.02 [0.80, 1.30]		1.14 [0.84, 1.56]	
Dementia	2.71 [1.15, 6.37]		2.64 [1.58, 4.42]		0.38 [0.09, 1.54]	
Comorbidity score						
0			-	-	-	
1	1.14 [0.90, 1.44]		1.06 [0.92, 1.22]		0.99 [0.82, 1.19]	
2	1.21 [0.91, 1.61]		1.04 [0.87, 1.24]		1.10 [0.88, 1.37]	
3+	1.27 [0.87, 1.84]		1.25 [0.99, 1.58]		0.87 [0.63, 1.21]	
Increase in score	1.09 [0.98, 1.21]	1.09 [0.96, 1.22]	1.05 [0.99, 1.12]	1.10 [1.02, 1.18]	0.99 [0.92, 1.08]	0.98 [0.89, 1.08]

\*Multivariate model for AST includes sex, age, alcohol group, WHR group and comorbidity score  
 \*\*Multivariate model for ALP includes sex, age, alcohol group and comorbidity score  
 \*\*\*Multivariate model for bilirubin includes sex, age, alcohol group, smoking group, WHR group and comorbidity score

**Table 3 Cox proportional hazards model for death (all-cause and cause-specific mortality) by AST test**

	Events	Person-years	Mortality rate (per 1000 person years)	Hazard ratio [95%CI]	Adjusted Hazard ratio* [95%CI]
<b>All-cause mortality</b>					
Normal AST	7319	77485	94.5	1	1
Abnormal AST	271	2586	104.8	1.11 [0.99, 1.26]	1.27 [1.09, 1.47]
Abnormal AST within 1x	229	2267	101.0	1.07 [0.92, 1.24]	1.17 [1.02, 1.34]
Abnormal AST over 2x	42	319	131.7	1.43 [1.04, 1.96]	1.62 [1.22, 2.16]
Hazard ratio for increase in AST abnormality group				1.12 [1.02, 1.24]	1.26 [1.12, 1.41]
<b>Cause-specific mortality</b>					
<b>CVD</b>					
Normal AST	3097	77485	40.0	1	1
Abnormal AST	109	2586	42.1	1.06 [0.87, 1.28]	1.15 [0.92, 1.44]
<b>Cancer (excluding liver cancer)</b>					
Normal AST	1359	77485	17.5	1	1
Abnormal AST**	63	2586	24.4	1.40 [1.09, 1.80]	1.56 [1.21, 2.01]
<b>Respiratory disease</b>					
Normal AST	1235	77485	15.9	1	1
Abnormal AST	33	2586	12.7	0.80 [0.57, 1.13]	1.03 [0.70, 1.52]
<b>Liver disease</b>					
Normal AST	38	77485	0.49	1	1
Abnormal AST	8	2586	3.09	6.28 [2.92, 13.5]	7.00 [2.88, 17.06]

\*adjusted for age, sex, comorbidity group, alcohol intake and WHR group.

\*\*Deaths from cancer in subjects with abnormal AST were digestive cancer (19), respiratory cancer (12), breast cancer (6), genitourinary cancer (9), and other cancers (17).



**Table 4 Cox proportional hazards model for death (all-cause and cause-specific mortality) by ALP test**

	Events	Person-years	Mortality rate (per 1000 person years)	Hazard ratio [95%CI]	Adjusted Hazard ratio* [95%CI]
<b>All-cause mortality</b>					
Normal ALP	7068	77752	90.9	1	1
Abnormal ALP	903	6503.9	138.8	1.58 [1.47, 1.69]	1.47 [1.35, 1.61]
Abnormal ALP within 1x	809	5895.7	137.2	1.56 [1.44, 1.68]	1.42 [1.32, 1.52]
Abnormal ALP over 2x	94	608.3	154.5	1.76 [1.44, 1.68]	1.44 [1.13, 1.84]
Hazard ratio for increase in ALP abnormality group				1.47 [1.39, 1.56]	1.37 [1.26, 1.48]
<b>Cause-specific mortality</b>					
<b>Cardiovascular disease</b>					
Normal ALP	3010	77752	38.7	1	1
Abnormal ALP	358	6504	55.0	1.46 [1.30, 1.62]	1.34 [1.17, 1.55]
<b>Cancer (excluding liver cancer)</b>					
Normal ALP	1324	77752	17.0	1	1
Abnormal ALP**	174	6504	26.8	1.61 [1.37, 1.89]	1.61 [1.39, 1.86]
<b>Respiratory disease</b>					
Normal ALP	1181	77752	15.2	1	1
Abnormal ALP	161	6504	24.8	1.68 [1.42, 1.98]	1.58 [1.32, 1.90]
<b>Liver disease</b>					
Normal ALP	35	77752	0.45	1	1
Abnormal ALP	13	6503.9	2.00	4.59 [2.43, 8.69]	5.95 [2.83, 12.51]

\*adjusted for age, sex, comorbidity group and alcohol intake.

\*\*Deaths from cancer in subjects with abnormal ALP were digestive cancer (51), respiratory cancer (26), skin cancer(5), breast cancer (15), genitourinary cancer (35), and other cancers (42).

**Table 5 Cox proportional hazards model for death (all-cause and cause-specific mortality) by bilirubin test**

	Events	Person-years	Mortality rate (per 1000 person years)	Hazard ratio [95%CI]	Adjusted Hazard ratio* [95%CI]
<b>All-cause mortality</b>					
Normal Bilirubin	7063	75176	94.0	1	1
Abnormal Bilirubin	416	4108.9	101.2	1.09 [0.99, 1.20]	1.15 [1.02, 1.30]
Abnormal bilirubin within 1x	388	3866	100.4	1.08 [0.98, 1.19]	1.14 [0.99, 1.29]
Abnormal bilirubin over 2x	28	242.8	115.3	1.24 [0.86, 1.79]	1.35 [0.91, 2.00]
Hazard ratio for increase in bilirubin abnormality group				1.09 [1.00, 1.18]	1.07 [0.98, 1.17]
<b>Cause-specific mortality</b>					
<b>Cardiovascular disease</b>					
Normal Bilirubin	2981	75176	39.7	1	1
Abnormal Bilirubin	190	4109	46.2	1.18 [1.02, 1.36]	1.15 [0.98, 1.36]
<b>Cancer (excluding liver cancer)</b>					
Normal Bilirubin	1331	75176	17.7	1	1
Abnormal Bilirubin**	69	4109	16.8	0.96 [0.75, 1.22]	0.90 [0.68, 1.19]
<b>Respiratory disease</b>					
Normal Bilirubin	1203	75176	16.0	1	1
Abnormal Bilirubin	58	4109	14.1	0.89 [0.68, 1.16]	0.97 [0.69, 1.35]
<b>Liver disease</b>					
Normal Bilirubin	44	75176	0.6	1	1
Abnormal Bilirubin	5	4109	1.22	2.11 [0.84, 5.32]	1.71 [0.63, 4.65]

\*adjusted for age, sex, comorbidity group, alcohol intake and smoking status.

\*\*Deaths from cancer in subjects with abnormal bilirubin were digestive cancer (22), respiratory cancer (11), breast cancer (7), genitourinary cancer (16), and other cancers (13).

**Table 6 Cox proportional hazards model for death (all-cause and cause-specific mortality) by multiple elevated tests**

	Events	Person-years	Mortality rate (per 1000 person years)	Hazard ratio [95%CI]	Adjusted Hazard ratio* [95%CI]
<b>All-cause mortality</b>					
Normal	6952	74068	93.9		
2 or more abnormal	134	950	141.1	1.55 [1.30, 1.83]	1.54 [1.30, 1.83]
<b>Cause-specific mortality</b>					
<b>Cardiovascular disease</b>					
Normal	2958	74068	39.9		
2 or more abnormal	46	950	48.4	1.24 [0.93, 1.66]	1.24 [0.88, 1.74]
<b>Cancer (excluding liver cancer)</b>					
Normal	1284	74068	17.3		
2 or more abnormal	34	950	35.8	2.11 [1.50, 2.97]	2.11 [1.59, 2.80]
<b>Respiratory disease</b>					
Normal	1169	74068	15.8		
2 or more abnormal	18	950	19.0	1.23 [0.77, 1.96]	1.23 [0.79, 1.90]
<b>Liver disease</b>					
Normal	38	74068	0.51		
2 or more abnormal	7	950	7.4	14.6 [6.5, 32.6]	17.0 [7.2, 40.2]

\*adjusted for age, sex and comorbidity group

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