Sixty per cent of persistent diarrhoea occurs before 6 months, and 90% below 1 year of age.[5] The percentile cut-offs are justified due to the lack of well-defined absolute values for deficient status, especially in children.[6] Since it was stated in an earlier report of this study that poor folate/cobalamin status was very prevalent in this study population, such an analysis based on absolute values might not have been possible. The sample size was large and so the probability of even a small difference being significant is high.

GEE logistic regression was aptly used here as this was a dataset with correlated responses and it seems all important confounders have been adjusted for, including zinc supplementation. Age as a predictor of acute/persistent diarrhoea has an adjusted OR close to null, which is also true for the association between high tHcy and acute diarrhoea. The temporality of association appears to be clear, as exposure was measured before outcome. Reverse causality has been mentioned as another explanation, i.e. before enrolment, a higher disease burden in these children would have led to folate deficiency, and only such children had developed diarrhoea during the study. In this study, data were available on self-reported diarrhoea only for 24 hours before inclusion. Since this was an *a priori* stated secondary objective, the possibility of reverse causality could have been anticipated, and comprehensive information collected on previous diarrhoeal morbidity rather than a 24-hour period. The exposure variables were measured objectively. However, as the outcome was measured as reported by the caregiver, this may have introduced information bias.

A memorandum of the WHO mentions that in northern India, 15% of children aged 0–35 months experienced persistent diarrhoea during one year of surveillance, and the case-fatality rate for such episodes was 14% compared with 0.7% for shorter episodes.[1] In a community-based study the incidence of persistent diarrhoea was found to be 6.3 per 100 child-years with the highest incidence in the age group of 0–11 months.[7] Up to 40% mortality associated with diarrhoeal disease is reported to be due to prolonged episodes and associated malnutrition.[5] Persistent diarrhoea alone amounts to 47% of diarrhoeal deaths in India.[8] The average cost of treatment of persistent diarrhoea was estimated to be US$ 10 in one study which is higher than that for shorter episodes.[9]

Intestinal mucosal damage and consequent problems with nutrient absorption are common features in all children with persistent diarrhoea, and therefore nutritional management is the cornerstone of treatment.[10–12] Improvements in nutritional status of infants and children as well as prevention and rational management of acute diarrhoea are keys to prevention of persistent diarrhoea.[13] With its vast numbers of malnourished children, persistent diarrhoea shall continue to be an important health problem in India. Any intervention that is implementable at the community level to prevent this condition should be welcome. Though evidence is at yet limited, the results of this study do arouse interest, and warrant further community-based research in this direction in India.

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RIZWAN S.A.
SANJEEV KUMAR GUPTA
Centre for Community Medicine
All India Institute of Medical Sciences
Ansari Nagar
New Delhi
sgupta_91@yahoo.co.in

Mortality and non-alcoholic fatty liver disease: Type of study cohort matters!

Lazo M, Hernaez R, Bonekamp S, Kamel IR, Brancati FL, Guallar E, Clark JM. (Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health; Department of Radiology, The Johns Hopkins University School of Medicine; Department of Medicine and Welch Center for Prevention, Epidemiology, and Clinical Research, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; Department of Cardiovascular Epidemiology and Population Genetics, National Center for Cardiovascular Research, Madrid, Spain.) Non-alcoholic fatty liver disease and mortality among US adults: Prospective cohort study. *BMJ* 2011;**343:**d6891 doi: 10.1136/bmj.d6891

SUMMARY

A large population-based cohort study was carried out on the basis of data collected during the NHANES III (Third, National Health and Nutrition Assessment Survey), which was used to find the association

between all-cause mortality and non-alcoholic fatty liver disease (NAFLD). The data were collected from a sample of United States' household population in a survey conducted between 1988 and 1994. This was connected to the mortality data collected after a median of 14.5 years (maximum 18 years) of 14 797 adults (>20 years of age) diagnosed with or without NAFLD at the time of the original survey.

The diagnosis of NAFLD was made on the basis of review of abdominal ultrasonography videos done at the time of the original survey for gallbladder disease. The fatty liver was graded as none to mild or moderate to severe. Subjects with raised ALT (defined as >40 IU/L for men and >31 IU/L for women) were labelled as having non-alcoholic steatohepatitis (NASH) whereas those with normal ALT were labelled as having pure fatty liver or NAFLD. Subjects with positive markers for hepatitis B, hepatitis C or iron overload were excluded. Further excluded were subjects with history of cardiovascular disease, history of cancer, cancer death within one year of start of follow-up, alcohol consumption in excess of 14 drinks per week for women and 21 drinks per week for men. After exclusion, data for 11 371 subjects (no fatty liver [*n*=8856]; NAFLD [*n*=2089]; NASH [*n*=426]) were available for analysis. The mortality data derived from the National Centre for Health Statistics database using the underlying cause of death (UCOD-113) codes. All-cause mortality, mortality from cardiovascular diseases, cancer- and liver-related, was evaluated. Cox proportional hazards regression analysis was used to calculate hazard ratios and 95% confidence intervals for deaths from all causes, cardiovascular disease, cancer and liver disease by hepatic steatosis status. Adjustment was done for sex and race or ethnicity in model one and further adjustment was done for education, smoking, alcohol consumption, physical activity, body mass index, hypertension, hypercholesterolaemia and diabetes in model two.

There were a total of 1836 (22%) events or deaths. No increased risk of death was shown in either NAFLD or NASH groups compared with controls (subjects without hepatic steatosis). As compared with controls, the hazard ratios for death among NAFLD and NASH subjects were 0.91 (95% CI 0.78–1.08) and 0.80 (0.53–1.22), respectively. Further, no difference was found in the hazard ratios for cause-specific mortality either. The fully adjusted hazard ratios in subjects with NAFLD or NASH compared with those without hepatic steatosis were 0.86 (0.67–1.12) and 0.59 (0.29–1.20) for cardiovascular disease, 0.92 (0.67–1.27) and 0.53 (0.26–1.10) for cancer, and 0.64 (0.12–3.59) and 1.17 (0.15–8.93) for liver disease. Neither NAFLD nor NASH were associated with increased mortality.

COMMENT

NAFLD is now considered to be one of the commonest causes of chronic liver disease in developed as well as developing countries. It is responsible for a large proportion of cases of asymptomatic transaminasemia, cryptogenic cirrhosis[1] and even liver cancer.[2] We have earlier shown that NAFLD is responsible for one-third of cases of asymptomatic rise in transaminases in India.[3] In a recently conducted population-based prevalence study of a rural population from West Bengal, India, the prevalence of NAFLD and NASH was found to be 8.7% and 2.3%, respectively. More disturbing was the prevalence of 0.2% of cryptogenic or NASH-related cirrhosis.[4] This becomes even more significant because of the rural background of this population. The prevalence of NAFLD-related chronic liver diseases would be expected to be considerably higher in the urban population of India. Further, with the increasing prevalence of metabolic syndrome and diabetes,[5] the prevalence of NAFLD is expected to rise in India.

This figure suggests a huge burden of end-stage liver disease and its complications in the years to come. In addition, the risk factors associated with NAFLD such as obesity, diabetes mellitus, hypertension and dyslipidaemia are also risk factors for cardiovascular disease. Therefore, it would seem logical to expect higher mortality from liver causes and cardiovascular events in patients suffering from NAFLD. Studies have shown that patients with NASH (the more severe form of NAFLD) have higher mortality as compared to the reference general population, and the most common causes of mortality are cardiovascular causes, malignancies and liver disease.

A Danish cohort study followed 7372 individuals with a discharge diagnosis of fatty liver (1770 of whom had NAFLD) and found that the mortality was 2.6-fold higher among patients with NAFLD as compared with the Danish general population.[6] However, these patients were picked up from hospital rather than from the general population. Another study included 129 patients who were referred for raised transaminases and fatty liver on liver biopsy and no history of significant alcohol intake with negative markers for hepatitis B, C and iron overload. After a mean follow-up of 13.7 years, patients with NASH were found to have a higher mortality as compared to the Swedish general population (p=0.01), whereas patients with pure fatty liver did not have a higher mortality. Again, the patients were referred, unwell patients and only the controls were derived from the general population.[7] Adams *et al*. studied 420 patients with a diagnosis of NAFLD, picked up from the medical register and followed up the cohort for 3192 person-years. The mortality of this cohort was found to be higher (standardize mortality ratio of 1.34; CI 1.003–1.76; p=0.03) compared with the mortality of the general population of Olmsted county, Minnesota. Even in this study, the subjects were patients with a diagnosis of NAFLD rather than asymptomatic patients picked up from the general population. Liver-related mortality was the third most common cause of death in the test population, preceded by cardiovascular causes and cancers.[8] Subjects, when recruited from the population in an asymptomatic stage are expected to have milder disease, whereas a cohort derived from hospital-based registries are expected to have more advanced disease. In the present study, the entire study population (controls as well as test cohort) was derived from the large population-based sample. There have been three other studies where the study cohort was derived from the NHANES III database, as in the present study.[9–11] However, the diagnosis of NAFLD in these studies was based on raised ALT levels in the absence of hepatitis B, hepatitis C, iron overload or hepatotoxic drug use. The diagnosis of NAFLD was confirmed by ultrasonography in the present study. Further, one of these studies did not establish any association of mortality with ALT elevation and another one demonstrated higher all-cause and cardiovascular mortality in patients with raised ALT only in the age group of 45–54 years.

Patients with pure fatty liver have not been shown to have higher mortality rates. One hundred and nine patients with pure fatty liver picked up on liver biopsy were linked to the Danish health registry to look for causes of death over a median follow-up of 16.7 years and these were compared with mortality data of the Danish general population. No increase in mortality was established.[12] A study by Teli *et al*. (over a median follow-up of 11 years) showed that pure fatty liver in 40 patients did not progress, suggesting a benign outcome.[13] However, in the present study, the mortality was similar in the group with NAFLD or NASH.

The present study, for the first time, using a population-derived large cohort with a considerable follow-up period of 18 years, demonstrated no increase in mortality among NAFLD subjects. So, an asymptomatic cohort of NAFLD derived from the

community, does not have higher mortality (all-cause, cardiovascular, cancer-related or liver-related). This is in contrast to other studies which used subjects with hospital-based diagnosis of NAFLD/NASH, or based only on the presence of raised ALT without ultrasound demonstration of fatty liver, where a higher mortality was demonstrated in subjects with NAFLD. In conclusion, asymptomatic NAFLD detected in the population may not be associated with higher mortality rates, whereas those who are symptomatic and detected during hospital visits are associated with higher mortality rates as compared to general/ reference population, reflecting selection bias. Thus, the variation in the type of cohorts studied is responsible for discrepancy in the results on mortality data in people with NAFLD.

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KAUSHAL MADAN
AYUSH DHINGRA
Medanta Institute of Digestive and Hepatobiliary Sciences
Medanta–The Medicity Hospital
Gurgaon, Haryana
k_madan_2000@yahoo.com