RESEARCH

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THIS WEEK'S RESEARCH QUESTIONS

Body mass index, alcohol, and liver disease

Bette Liu and colleagues analysed data from the Million Women Study and report that, compared with women with a body mass index between 22.5 and 25, those who were overweight or obese had an increased risk of liver cirrhosis (p 633). The risk increased by about 28% for each five unit increase in BMI. For women who said they had around two and a half alcoholic drinks a day the absolute risk with increasing BMI was substantially greater than for those who admitted to about half a standard drink a day.

Carole Hart and colleagues looked at Scottish men and found that being overweight or obese and consuming 15 or more units per week of alcohol led to a greater risk of dying of liver disease (p 634). The excess risk due to BMI was small compared with that due to alcohol, but the relative excess risk due to interaction was large. The authors note that their findings might underestimate the absolute risk of liver disease.

In their editorial Christopher Byrne and Sarah Wild warn that "reducing alcohol consumption and obesity are, at present, our only weapons against non-viral liver disease. The progression of non-alcoholic fatty liver disease to end stage liver disease can now be added to the list of the undesirable consequences of modern lifestyles" (p 606).

CNRI/SPL

Controversy of the week 1: which underweight African neonates might live longer if given vitamin A supplements?

AMI VITALE/PANOS

As editorialist Andrew Prentice points out, dietary supplementation with vitamin A for children aged 6 to 60 months reduces child mortality by 30% in countries with evidence of at least marginal deficiency, a policy recommended by WHO and widely adopted worldwide (p 607). But the jury is out on whether to give vitamin A at birth. While three trials—all done in Asia—have shown that it reduces infant mortality, two trials in Africa and one small trial in Nepal have found no beneficial effect. Christine Stabell Benn and colleagues deepen this debate by reporting the results of a randomised, placebo controlled, two by two factorial trial in Guinea-Bissau in which around 1700 neonates weighing less than 2.5 kg were assigned to 25 000 IU vitamin A or placebo, as well as to early BCG vaccine or the usual late BCG (p 636). They found no evidence for interaction between vitamin A supplementation and BCG vaccination, and the "early BCG" versus "no early BCG" part of the trial will be presented elsewhere. In this paper they analyse the new trial data along with the results of one of the earlier African trials, conducted by this same team with normal weight neonates. Their overall conclusion is that vitamin A supplementation at birth was not associated with lower mortality in low birthweight neonates. And, worryingly, supplementation was associated with 41% increased mortality in girls.

LATEST RESEARCH: For these and other new research articles see http://www.bmj.com/channels/research.dtl

Sunbed use in teenagers In an analysis of survey data, Catherine S Thomson and colleagues aimed to quantify and characterise the use of sunbeds by young people in England. In their paper, published online this week, they report that 6% of teenagers across the country had used a sunbed, but this figure rose to around 50% in girls aged 15-17 in Liverpool and Sunderland. Nearly a quarter of children said their sunbed use had been unsupervised. The authors say that their findings indicate a health risk that needs to be controlled by national legislation aimed at sunbed outlets.

Slideshow: How to get your research published in the *BMJ* In this slideshow three of the *BMJ*'s senior research editors give insiders' tips on how to focus your research question, write a great paper, and maximise your chances of getting it published (www.bmj.com/video/how-to-write.dtl).

Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study

Bette Liu, Angela Balkwill, Gillian Reeves, Valerie Beral, on behalf of the Million Women Study Collaborators

EDITORIAL by Byrne and Wild
RESEARCH, p 634

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STUDY QUESTION What is the relation between body mass index and incident liver cirrhosis, and what contribution do body mass index and alcohol consumption make to the incidence of liver cirrhosis in middle aged UK women?

SUMMARY ANSWER Excess body weight increases the risk of liver cirrhosis by 28% for each 5 unit increase in body mass index. Among women who drink about half an alcoholic drink a day, 0.8 in 1000 with a healthy weight will be admitted to hospital with or die from cirrhosis over five years compared with 1.0 in 1000 women who are obese; in those who drink an average of two and a half alcoholic drinks a day, the corresponding rates are 2.7 in 1000 and 5.0 in 1000.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Although alcohol is a major cause of liver cirrhosis, recent evidence suggests that excess body weight may also play a role. Among middle aged women in the UK, excess body weight contributes to almost 20% of the cirrhosis related hospital admissions and deaths, and alcohol contributes to almost 50%.

Participants and setting
This study involved participants in the Million Women Study, which recruited 1.3 million UK women from 1996 to 2001 and followed them by record linkage to routinely collected National Health Service data on hospital admissions and deaths due to cirrhosis of the liver.

Design, size, and duration
This prospective cohort study examined data from 1 230 662 women who had no record of liver disease before recruitment. Women were followed for an average of 6.2 years, and during this period 1811 women were admitted to hospital with liver cirrhosis or died from cirrhosis.

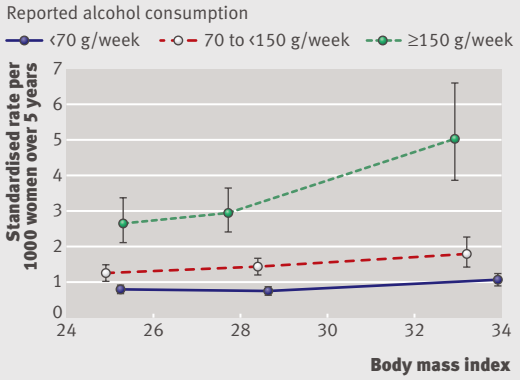
Main results and the role of chance
Among women with a body mass index of 22.5 or above, increasing body mass index was associated with an increased incidence of liver cirrhosis. The adjusted relative risk was 1.28 (95% confidence interval 1.19 to 1.38; P<0.001) for each 5 unit increase in body mass index. The relative risk of liver cirrhosis did not differ significantly according to the amount of alcohol consumed, but the absolute risk did. Among women who reported drinking less than 70 g alcohol per week (mean intake 0.4 drinks a day), over five years 0.8 in 1000 with a healthy weight and 1.0 in 1000 who were obese were admitted to hospital with cirrhosis or died from cirrhosis. The corresponding figures in women drinking 150 g or more of alcohol per week (mean intake 2.5 drinks a day) were 2.7 (2.1 to 3.4) and 5.0 (3.8 to 6.6). We estimate that in middle aged women in the UK, approximately 42% of hospital admissions with cirrhosis or deaths from cirrhosis can be attributed to alcohol consumption and 17% to excess body weight (body mass index ≥25).

Bias, confounding, and other reasons for caution
Information on body mass index and alcohol consumption was based on self report.

Generalisability to other populations
Although obesity and alcohol intake both affect the risk of a woman developing cirrhosis, their contributions to incidence rates of cirrhosis in other populations will differ depending on the person's age, sex, body mass index, and alcohol consumption.

Study funding/potential competing interests
The study was funded by Cancer Research UK and the UK Medical Research Council.

STANDARDISED RATES (WITH 95% CI) FOR LIVER CIRRHOSIS PER 1000 WOMEN OVER 5 YEARS BY BODY MASS INDEX AND ALCOHOL CONSUMPTION



Rate plotted against mean measured body mass index (BMI) in each BMI category

BMJ pico: advice to authors

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This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c912

Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies

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EDITORIAL by Byrne and Wild
RESEARCH, p 633

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STUDY QUESTION Do raised body mass index (BMI) and alcohol consumption act together to increase liver disease risk?

SUMMARY ANSWER Raised BMI and alcohol consumption are both related to liver disease, with a supra-additive interaction between the two.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Alcohol consumption is well known to be linked to liver disease. Recent evidence suggests that raised BMI is also associated with liver disease. This study showed that both alcohol consumption and high BMI were associated with liver disease and their combined effect was greater than the sum of their separate effects.

Participants and setting

Participants were 9559 men from two of the Scottish Midspan prospective cohort studies.

Design, size, and duration

Men were screened between 1965-68 (Main study) and 1970-73 (Collaborative study) and followed up for liver disease mortality or morbidity until 31 December 2007 (median 29 years, maximum 42 years). BMI was grouped as underweight/normal weight, overweight, or obese according to WHO categories, and alcohol consumption as none, 1-14, and 15 or more units per week (where 1 unit=8 g ethanol). Men were grouped by a combination of their BMI and alcohol consumption categories together, and risk of liver disease was compared across these nine groups.

Main results and the role of chance

BMI and alcohol consumption were each strongly related to liver disease mortality (P=0.001 and P<0.0001, respectively). Drinkers of 15 or more units per week of alcohol in any BMI category, and obese drinkers, had high relative rates of liver disease mortality or morbidity compared with underweight/normal weight non-drinkers. Drinkers of 15 or more units per week had adjusted relative rates for liver disease mortality of 3.16 (95% confidence interval 1.28 to 7.8) for underweight/normal weight, 7.01 (3.02 to 16.3) for overweight, and 18.9 (6.84 to 52.4) for obese men. The relative rate for obese men consuming 1-14 units per week was 5.3 (1.36 to 20.7). The relative excess risk due to interaction between BMI and alcohol consumption was 5.58 (1.09 to 10.1); synergy index 2.89 (1.29 to 6.47). The combination of high BMI (overweight or obese) and high alcohol consumption (15 or more units per week) was greater than the additive effect of the two separately after adjustment for risk factors (age, study, social class, smoking, height, bronchitis, FEV_1, angina, ischaemia on electrocardiogram, and diabetes) (figure).

Bias, confounding, and other reasons for caution

Individuals' BMIs and alcohol consumption could have changed over the follow-up period, although such changes are unlikely to have affected the reported interaction. Weight and height were self-reported in the Main study whereas they were measured in the Collaborative study, but this difference is unlikely to have affected our conclusions since similar results were obtained when the studies were analysed separately.

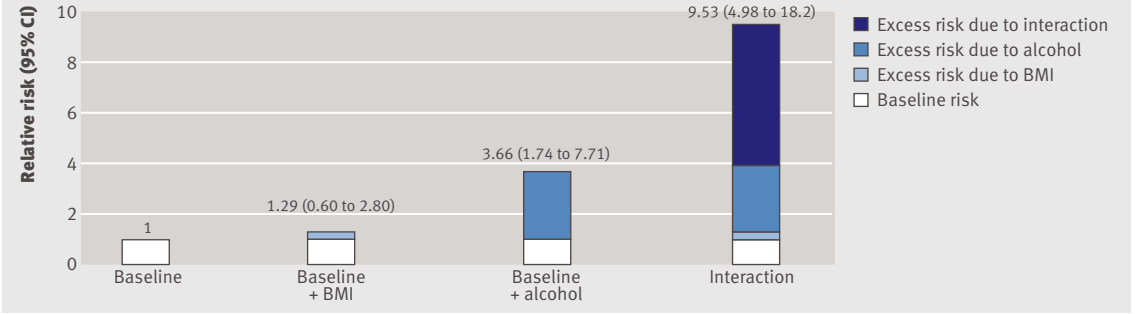
Generalisability to other populations

As most of the men were from working populations, and therefore healthier on average than general populations, the results may underestimate absolute risk of liver disease, although the relative risks are likely to be generalisable to male populations from similar contexts.

Study funding/potential competing interests

This research was supported by the Chief Scientist Office of the Scottish government, grant number CZG/2/421. GDB is a Wellcome Trust Fellow (WBS U.1300.00.006.00012.01). The authors declare no other competing interests.

CONTRIBUTIONS OF BMI AND ALCOHOL TO LIVER DISEASE MORTALITY



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Rapid testing for malaria in settings where microscopy is available and peripheral clinics where only presumptive treatment is available: a randomised controlled trial in Ghana

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response on bmj.com

"Introducing rapid diagnostic tests requires an in depth change to the provider's diagnosis and treatment concepts and represents a new approach to managing patients, especially in the event of a negative test. This can only be achieved in a supportive environment that constantly and consistently reinforces the new approach"
Valérie D'Acremont, consultant in tropical and infectious diseases, Swiss Tropical and Public Health Institute, Switzerland, in a rapid response

STUDY QUESTION What impact do rapid diagnostic tests have on prescribing of antimalarials and antibiotics in West Africa, both in settings where microscopy is used for the diagnosis of malaria and in clinical (peripheral) settings that rely on clinical diagnosis?

SUMMARY ANSWER In peripheral settings where microscopy was not available, rapid diagnostic tests led to a significant reduction in overprescription of antimalarials and better targeting of antibiotics; however, rapid diagnostic tests had little impact on prescribing in settings with microscopy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Rapid diagnostic tests are sensitive and specific for malaria, but data from East Africa suggests their impact on prescribing is often limited. In this West African setting, the tests significantly improved prescribing for patients with possible malaria, but only in settings there were no microscopy facilities.

Design
We ran a randomised, controlled, open label trial from Aug 2007 to Dec 2008.

Participants and setting
Participants were children and adults with suspected malaria presenting to one of four clinics in the rural Dangme West district of southern Ghana, one in which microscopy is used for diagnosis of malaria ("microscopy setting") and three where microscopy is not available and diagnosis of malaria is made on the basis of clinical symptoms ("clinical setting"). In each setting patients were randomly assigned either to a rapid diagnostic test or to the current diagnostic method at the clinic (microscopy or clinical diagnosis). A blood sample for a research microscopy slide was taken for all patients.

Primary outcome
The primary outcome was the prescription of antimalarials to patients of any age whose double read research slide was negative for malaria. The major secondary outcomes were the correct prescription of antimalarials, the impact of test results on antibiotic prescription, and the correct prescription of antimalarials in children under 5 years.

Main results and the role of chance
Of the 9236 patients screened, 3452 were randomised in the clinical setting and 3811 in the microscopy setting. Follow-up to 28 days was 97.6% (7088/7263). In the microscopy setting, 722 (51.6%) of the 1400 patients with negative research slides in the rapid diagnostic test arm were treated for malaria compared with 764 (55.0%) of the 1389 patients in the microscopy arm (adjusted odds ratio 0.87, 95% CI 0.71 to 1.1; P=0.16). In the clinical setting, 578 (53.9%) of the 1072 patients in the rapid diagnostic test arm with negative research slides were treated for malaria compared with 982 (90.1%) of the 1090 patients with negative slides in the clinical diagnosis arm (odds ratio 0.12, 95% CI 0.04 to 0.38; P=0.001). The use of rapid diagnostic tests led to better targeting of antimalarials and antibiotics in the clinical but not the microscopy setting, in both children and adults.

Harms
There were no deaths in children under 5 years at 28 days follow-up in either arm. There was no evidence using rapid diagnostic tests led to harm to children.

Bias, confounding, and other reasons for caution
Our study was a randomised trial with no evidence of unbalanced arms and patients characteristics were evenly distributed at baseline, so the likelihood of bias is minimal. Prescribers may have behaved differently because a trial was being conducted.

Generalisability to other populations
Our results are likely to be generalisable to other rural settings in West Africa. Our results are consistent with data from East Africa that show a limited impact of rapid diagnostic tests where microscopy exists.

Study funding/potential competing interests
This study was supported by the Gates Malaria Partnership and the ACT Consortium, with funds from the Bill & Melinda Gates Foundation. The sponsor and funder had no part in design, conduct, analysis, or interpretation of the trial. CJMW has received research funding for investigator initiated research from Pfizer and GlaxoSmithKline; no other author has conflicts of interest to declare.

Trial registration number
ClinicalTrials.gov NCT00493922

PRESCRIBING OF ANTIMALARIALS AND ANTIBIOTICS

	Health centre with microscopy		Health facilities with no microscopy	
	Rapid diagnostic test arm	Microscopy arm	Rapid diagnostic test arm	Clinical diagnosis arm
Patients treated with antimalarials				
Positive research slide	462/496 (93.2%)	458/511 (89.6%)	626/647 (96.8%)	616/633 (97.3%)
Negative research slide	722/1400 (51.6%)	764/1389 (55.0%)	578/1072 (53.9%)	982/1090 (90.1%)
Patients treated with antibiotics				
Positive research slide	67/496 (13.5%)	67/511 (13.1%)	87/647 (13.4%)	102/633 (16.1%)
Negative research slide	374/1400 (26.7%)	383/1389 (27.6%)	370/1072 (34.5%)	282/1090 (25.9%)
Correct treatment of malaria	1140/1896 (60.1%)	1085/1900 (57.1%)	1123/1719 (65.3%)	724/1723 (42.0%)

FAST TRACK

Vitamin A supplementation and BCG vaccination at birth in low birthweight neonates: two by two factorial randomised controlled trial

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EDITORIAL by Prentice

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STUDY QUESTION What is the effect of vitamin A supplementation and BCG vaccination at birth in low birthweight neonates in Guinea-Bissau?

SUMMARY ANSWER Vitamin A supplementation at birth was not associated with lower mortality in low birthweight neonates; however, vitamin A supplementation tended to be beneficial in boys but potentially harmful in girls.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Six trials of neonatal vitamin A supplementation have shown divergent results with respect to the impact of supplementation on mortality. The combined results of this trial and a complementary trial among normal birthweight neonates show that, overall, it would not be beneficial to implement a neonatal vitamin A supplementation policy in Guinea-Bissau, but the effect of neonatal vitamin A differs significantly by sex.

Design
This study was a randomised, placebo controlled, two by two factorial trial. Participants were randomly assigned to 25 000 IU vitamin A or placebo, as well as to early BCG vaccine or the usual late BCG vaccine.

Participants and setting
A total of 1717 neonates who weighed less than 2.5 kg and were born at the national hospital in Bissau, the capital of Guinea-Bissau, took part in this study. Infants were visited at home within the first 3 days and at 2, 6, and 12 months of age.

Primary outcome(s)
Mortality, calculated as mortality rate ratios (MRRs), after follow-up to 12 months of age for infants who received vitamin A compared with those who received placebo.

Main results and the role of chance
A total of 161 participants died between enrolment and their first birthday. Our analysis controlled for randomisation to "early BCG" or "no early BCG" showed that vitamin A supplementation at birth was not associated with lower mortality than placebo (MRR 1.08, 95% CI 0.79 to 1.47). There was a significant interaction between vitamin A supplementation and sex: the effect of vitamin A supplementation seemed to be beneficial in boys (MRR 0.74, 95% CI 0.45 to 1.22) but not in girls (MRR 1.42, 95% CI 0.94 to 2.15). When we incorporated the results of the present vitamin A supplementation trial in low birthweight neonates with those from our complementary trial in normal birthweight neonates in Guinea-Bissau, the combined MRR for the effect of neonatal vitamin A supplementation was 1.08 (95% CI 0.86 to 1.34); 0.80 (95% CI 0.58 to 1.10) in boys and 1.41 (95% CI 1.04 to 1.90) in girls.

Harms
On the basis of the two trials from Guinea-Bissau, vitamin A supplementation in neonates is associated with 41% increased mortality among girls.

Bias, confounding, and other reasons for caution
Several subgroup analyses were conducted and the results of these analyses should be interpreted with caution. The combined analysis of the two separate trials cannot be considered equivalent to a single trial enrolling both low birthweight and normal birthweight neonates and randomising them to the same type of treatment at the same time.

Generalisability to other populations
Seven trials, including this trial, have studied the effect of neonatal vitamin A supplementation on mortality. Three of the four trials from Asia found a beneficial effect, whereas the three trials from Africa found no beneficial effect. These divergent results could be owing to differences in the prevalence of vitamin A deficiency in the two regions. It seems that other environmental factors as well as sex may modify the effect of vitamin A supplementation, making it impossible to predict outcome on the basis of the pre-existing degree of vitamin A deficiency alone.

Study funding/potential competing interests
The study was funded by the EU, the Danish Medical Research Council, University of Copenhagen, March of Dimes, the Ville Heise Foundation, DANIDA, the Danish National Research Foundation, and the Novo Nordisk Foundation. The authors have no competing interests.

Trial registration number
ClinicalTrials.gov NCT00168610.

EFFECT OF VITAMIN A SUPPLEMENTATION AT BIRTH ON INFANT MORTALITY

	Vitamin A supplementation		Placebo		
	Total n	Mortality per 1000 person years (deaths/ person years)	Total n	Mortality per 1000 person years (deaths/ person years)	Mortality rate ratio* (95% CI)
All children	854	110 (83/757)	863	102 (78/762)	1.08 (0.79 to 1.47)
Stratified by BCG vaccination					
"Early BCG"	431	98 (38/386)	431	86 (33/384)	1.14 (0.71 to 1.84)
"No early BCG"	423	121 (45/371)	432	119 (45/378)	1.02 (0.67 to 1.56)
Interaction					P=0.73
Stratified by sex					
Boys	362	86 (28/325)	394	118 (41/349)	0.74 (0.45 to 1.22)
Girls	492	127 (55/432)	467	89 (37/414)	1.42 (0.94 to 2.15)
Interaction					P=0.046

*Adjusted for sex (except for sex stratified analyses) and randomisation to "early BCG" or "no early BCG."