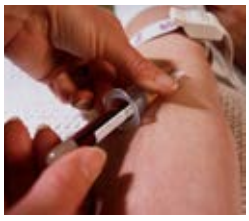
research

Alcohol consumption positively associated with non-fatal stroke p 311

Lyme neuroborreliosis has little effect on survival, wellbeing, or social parameters p 312



Point-of-care natriuretic peptide testing could help rule out heart failure p 314

Postmarketing needs for drugs often only briefly described in public documents p 314

ORIGINAL RESEARCH EPIC-CVD case-cohort study

Alcohol intake in relation to non-fatal and fatal coronary heart disease and stroke

Ricci C, Wood A, Muller D, et al

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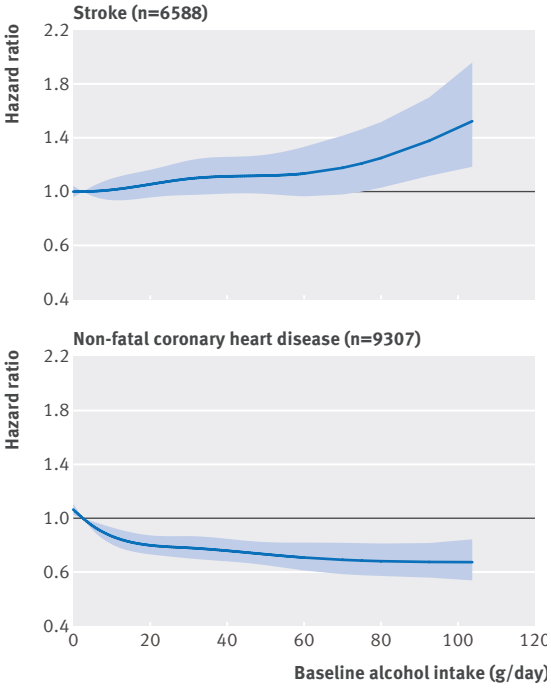
Find this at: http://dx.doi.org/10.1136/bmj.k934

Study question Is there an association between baseline and lifetime consumption of alcohol and fatal and non-fatal coronary heart disease (CHD) and stroke?

Methods A case-cohort study within the European Prospective Investigation into Cancer and nutrition (EPIC) cohort. A random subcohort of 16 244 EPIC participants and 17 594 incident CHD and stroke events identified between March 1991 and December 2010 were included. Of the 11 006 CHD cases, 9307 were non-fatal and 1699 were fatal. Of the 6588 stroke (including ischaemic and haemorrhagic stroke) events, 5855 were non-fatal and 733 were fatal. The median age at recruitment to the subcohort was 52 years, and the average follow-up time was 12.5 years.

Study answer and limitations Baseline and lifetime alcohol consumption were inversely related to non-fatal CHD risk, with hazard ratios of 0.94 per 12 g/day increase (95% confidence interval 0.92 to 0.96, P<0.001 for trend) and 0.97 (0.94 to 0.99, P=0.01 for trend), respectively. A J-shaped relation was observed for fatal CHD risk. Alcohol consumption was positively associated with the risk of non-fatal stroke and was consistent for ischaemic and haemorrhagic stroke. Misclassification of alcohol exposure and potential residual confounding in observational investigations may have biased the observed associations.



Association between baseline alcohol consumption (g/day) and risk of non-fatal and fatal coronary heart disease

What this study adds Based on a sizeable number of cardiovascular disease events from a large European prospective study, dose-response evaluations indicated that alcohol consumed during lifetime and assessed at baseline were inversely related to the risk of non-fatal CHD, and positively associated with the risk of non-fatal stroke.

Funding, competing interests, data sharing
See full paper on bmj.com

Reassurance for patients with Lyme neuroborreliosis

ORIGINAL RESEARCH Nationwide population based cohort study

Long term survival, health, social functioning, and education in patients with European Lyme neuroborreliosis

Obel N, Dessau RB, Krogfelt KA, et al

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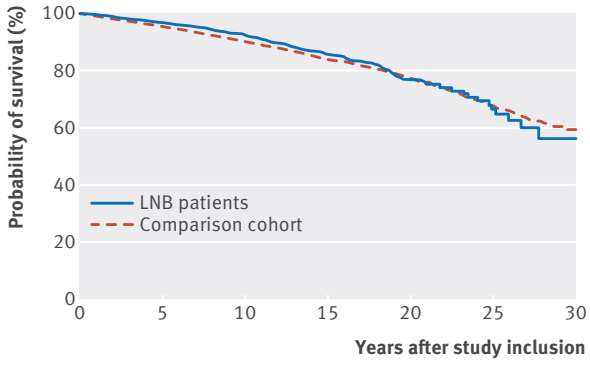
Find this at: http://dx.doi.org/10.1136/bmj.k1998

Study question What is the long term outcome in patients with Lyme neuroborreliosis?

Methods This was a nationwide population based cohort study using national registers. A collaboration with every Danish microbiology laboratory allowed identification of all Danish residents diagnosed as having Lyme neuroborreliosis during 1986-2016 (n=2067). This cohort was compared with a general population cohort matched on sex and date of birth (n=20 670). Effect on survival, health, and educational/social functioning was calculated as mortality rate ratios, incidence rate ratios, and differences in educational and social outcomes.



No at risk

LNB patients	2067	1653	1198	624	174	44	6
Comparison cohort	20 670	16 336	11 830	6180	1821	425	56

Cumulative survival of 2067 patients with Lyme neuroborreliosis (LNB) and 20 670 members of population comparison cohort

COMMENTARY Good outlook for patients with confirmed Lyme neuroborreliosis

Obel and colleagues report on one of the largest, and highest quality longitudinal follow-up studies to date of people with neurological forms of Lyme disease.[1] The study included more than 2000 people with neuroborreliosis and 20 000 controls, and the data are reassuring. If you are a patient with a confirmed microbiological diagnosis and neurological symptoms of Lyme disease, this will have no effect on your survival, wellbeing (health status), or social parameters (such as education, marriage and divorce rates) 10 years after your diagnosis compared with a control population.

This means that you will be able to recover fully and lead a normal working life, although if you are an adult you may have marginally less income and activity in the labour market than you did before the infection (rather than in comparison with the control population). Development, health, and educational achievement were not different in children diagnosed as having neuroborreliosis compared with controls. A moderately increased risk of non-melanotic skin cancer in people with neuroborreliosis compared with controls is probably explained by outdoor lifestyles that also lead to people becoming infected with Lyme disease. The finding of a rise in haematological malignancy in people who have had neurological forms of Lyme disease needs further investigation; however, reassuringly, although neuroborreliosis is associated with an increased risk of haematological cancer, it does not affect risk of death from these cancers.

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Poor evidence

This study is an exception in the evidence available to guide the care of people with Lyme disease. The development of the recent NICE guideline in which we were involved was marked by most of the evidence we reviewed being rated as very low or low quality under internationally accepted criteria.[2 3] Why has evidence generation been so poor until now? It cannot simply be that the disease has variable epidemiology and incidence between geographical areas.

Unlike in trials for other diseases, Lyme disease "experts" have failed to come together regionally, nationally, or internationally to conduct studies to an agreed set of core outcomes. When investigating new diagnostic technologies, research teams or manufacturers have been selective and inconsistent in the choice of inclusion and exclusion criteria and diagnostic outcomes. Results of small series testing new diagnostic technologies are quoted or used in clinical practice before wider evaluation in well designed trials. Specifically, a recent European consensus position statement on the diagnostic options available for Lyme disease states that no new reliable and clinically relevant tests are available other than serology and direct detection techniques and that cellular tests such as lymphocyte transformation or activation tests should not be used until they have been adequately assessed.[4]

Most clinical trials of new treatments for Lyme disease have different inclusion and exclusion criteria, and often no clarity exists about what does and does not comprise a diagnosis to enter the study or what is meant by "cure" or "ongoing symptoms." The selection of investigational agents and comparators often seems to be based on anecdote and personal practice.[5] The level of evidence in some important areas consists only of case series from which no firm conclusions can be drawn. Where better quality trials have been conducted,[6] many clinicians do not seem to accept the suggestion that long term treatments do not benefit

Study answer and limitations Mortality was not higher among patients with Lyme neuroborreliosis than in the comparison cohort (rate ratio 0.90, 95% confidence interval 0.79 to 1.03), but the patients had an increased risk of haematological (3.07, 2.03 to 4.66) and non-melanoma skin cancers (1.49, 1.18 to 1.88). At diagnosis, patients with Lyme neuroborreliosis had slightly higher employment and lower disability pension rates than people in the comparison cohort. After five years, patients and comparison cohort members had similar numbers of hospital contacts, employment rates, income, days of sick leave, rates of receipt of disability pension, and number of children. More patients were married and had completed high school. The registry based design precluded access to data on cerebrospinal fluid leucocyte counts, so the effect of this parameter on long term outcome could not be determined.

What this study adds A verified diagnosis of Lyme neuroborreliosis has no substantial effect on long term survival, health, or educational/social functioning. Nevertheless, the diagnosis decreases labour market involvement marginally and is associated with increased risk of haematological and non-melanoma skin cancers.

Funding, competing interests, data sharing The study was sponsored by the Danish Council for Independent Research. HTS was supported by the PROCRIN programme. KH has received royalties from Thermo Fisher.

The study has shown that good quality, large scale research can be conducted in Lyme disease

patients and have been hesitant to translate these findings into clinical practice.

Many clinicians and the public have enormous sympathy for people with symptoms but without a formal diagnosis. Old fashioned medical dogmatism ("you can't have Lyme disease as the tests are negative") have left many patients feeling that they have not had the correct tests or treatments.[7 8]

In many cases, these people have a point: they have not been listened to, and other equally dogmatic practitioners are happy to provide clarity for often high cost but poorly evidenced services. Obel and colleagues' work offers a positive outlook for patients treated promptly on diagnosis, so it is important for primary and secondary care clinicians to consider neuroborelliosis when the history, symptoms, or signs implicate Lyme disease in the differential diagnosis.[9]

The study has shown that good quality, large scale research can be conducted in Lyme disease. It gives us hope that large scale research on the epidemiology, diagnosis, and treatment is possible. A core outcome set would be a good place to start, alongside robust multi-region epidemiological studies to establish diagnostic criteria robust enough to use across multicentre clinical trials.

This study did not include patients in the design, analysis, or reporting, and future research should have more active patient involvement. We might then be able to know for certain which tests can reliably rule in or rule out a diagnosis of Lyme disease and which antibiotics to prescribe for confirmed infections, at which dose, and for how long.[10]

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Find the full version with references at http://dx.doi: 10.1136/bmj.k2284

AUTHORS' PERSPECTIVE

Niels Obel, Anne-Mette Lebech, and Ram B Dessau

How unique Danish registry data can benefit patients

Lyme borreliosis is a common tickborne infection. When the disease causes neurological symptoms (often facial paralysis), it gives rise to major concern. Patients ask: "Can you treat me and get me back to my daily life?" In our more than 30 years of experience in infectious diseases, we have not been able to give good answers to these questions. Some scientific literature seems to emphasise the frequency and severity of long term complications. Most existing research looks at small patient populations with no control cohorts.

We have previously used Danish registers to study the long term outcomes of infections of the central nervous system (CNS). These studies showed CNS infections were associated with substantially decreased employment, lower education, and increased need for disability pension. Inspired by these studies, we linked national registers with local registers of Lyme borreliosis tests. We found that most people continue their usual life after being treated for Lyme neuroborreliosis.

An important aspect of the paper was access to data from national Danish registries. Denmark has a tax funded public health system and its registry allowed us to undertake a population based nationwide study including more than 2000 patients and a well designed control population.

Surprisingly, our study showed an association between a diagnosis of Lyme neuroborreliosis and haematological cancer and skin cancer. We believe this to be a true association, but cannot exclude the possibility it is a random finding. Our hypothesis is that the association is caused by a common risk factor, rather than a consequence of infection with Borrelia.

We are aware that Lyme disease may give rise to residual symptoms which infrequently lead to social consequences. However, access to subjective information on the internet can induce anxiety. We find that a main objective for modern epidemiology is to use patient data to reassure patients of a benign prognosis, when justified. Danish registry data are probably the best in the world for this. Currently, Danish authorities are discussing reducing researchers' access to these data, which would be a regressive move.

We can use the results of the study in our daily clinical work to provide answers to patients: "Yes, neuroborreliosis is a severe and unpleasant disease, but it can be treated, and almost all patients get back to their daily lives."

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Ram B Dessau is a doctor at the Department of Clinical Microbiology and Infectious Diseases, Aalborg University Hospital, Denmark

ORIGINAL RESEARCH Systematic review and meta-analysis

Diagnostic accuracy of point-of-care natriuretic peptide testing for chronic heart failure in ambulatory care

Taylor KS, Verbakel JY, Feakins BG, et al
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Find this at: http://dx.doi.org/10.1136/bmj.k1450

Study question How accurate are point-of-care natriuretic peptide tests for chronic heart failure in ambulatory care?

Methods The authors carried out a systematic review and meta-analysis of data from diagnostic accuracy studies. The population was patients with suspected or confirmed chronic heart failure. The index tests were point-of-care ones for B-type natriuretic peptide (BNP) or N terminal fragment pro B-type natriuretic peptide (NTproBNP), and these were compared with echocardiography, clinical examination, or combinations of these. The target condition was chronic heart failure.

Study answer and limitations Forty two publications of 39 individual studies met the inclusion criteria and 40 publications of 37 studies were included in analysis. Of the 37 studies, 30 evaluated point-of-care testing for BNP and seven for NTproBNP. 15 studies were done in ambulatory care settings in populations with a low prevalence of chronic heart failure. Five studies were done in primary care. The authors found that BNP had variable ability to rule out chronic heart failure at low cut-off values, but the threshold for NTproBNP of 135 pg/mL recommended by the European Society of Cardiology for non-acute care might be appropriate for point-of-care testing in this setting (sensitivity 0.95, 95% confidence interval 0.90 to 0.98; specificity 0.60, 95% confidence interval 0.44 to 0.74). Data were limited, in particular for primary care studies and for NTproBNP.

What this study adds The findings of this review suggest that point-of-care natriuretic peptide testing could help doctors in ambulatory care settings to rule out patients with heart failure, but this needs to be confirmed by further studies. As with hospital based natriuretic peptide testing, positive results need to be confirmed by other tests.

Funding, competing interests, data sharing
This study was funded by grants from the National Institute for Health Research. See the full paper on bmj.com for details of competing interests. No additional data are available.

ORIGINAL RESEARCH Cross sectional analysis

Postmarket studies required by the US Food and Drug Administration for new drugs and biologics approved between 2009 and 2012

Wallach JD, Egilman AC, Dhruva SS, et al
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Find this at: http://dx.doi.org/10.1136/bmj.k2031

Study question What are the characteristics of the FDA postmarketing requirements, and what are the rates of registration and results reporting on ClinicalTrials.gov and publication in peer reviewed journals of required prospective cohort studies, registries, and clinical trials?

Methods Postmarketing requirements known at the time of FDA approval (including FDA authority, study design, and study characteristics) for all new drugs and biologics approved in 2009-12 were characterised by use of publicly available FDA documents. ClinicalTrials.gov, PubMed, and Scopus were searched for registration records, reported results, and publications in peer reviewed journals for all required prospective cohort studies, registries, and clinical trials.

Study answer and limitations Between 2009 and 2012, the FDA approved 97 new drugs and biologics for 106 indications with at least one postmarketing requirement at the time of first approval (437 postmarketing requirements in total). Many postmarketing requirements were briefly described (median word count of 44 (interquartile range 29-71)) and often lacked information to determine an up to date progress (131 (30%)). Of 134 postmarketing requirements for prospective cohort studies, registries, and clinical trials, 102 (76%) were registered on ClinicalTrials.gov; 47 (72.3%) of 65 completed studies had either reported results on ClinicalTrials.gov or were published a median of 47 (32-67) months after FDA approval. Similar registration and reporting rates were observed in clinical trials only. Publicly available data sources used in the study contains limited information, which made categorising and determining ClinicalTrials.gov registrations and publications difficult.

What this study adds Postmarketing requirements for drugs and biologics are often briefly described in public documents, without enough information to determine the required study characteristics. Although three quarters of postmarketing requirements for prospective cohort studies, registries, and clinical trials were registered on ClinicalTrials.gov, at least one quarter of required studies for which results reporting or publication would be expected have not been publicly disseminated.

Results reporting and publication of postmarketing requirements of new drugs and biologics approved by the FDA between 2009 and 2012. Data are number or number (%) of required studies

	Publication or results reporting*		
Category	Eligible for publication	Published	Results reported or published
Prospective cohort studies, registries, and clinical trials	65	37 (56.9)	47 (72.3)
Authority:			
FDAAA	37	22 (59.5)	28 (75.7)
PREA	22	11 (50.0)	15 (68.2)
Accelerated approval	6	4 (66.7)	4 (66.7)

FDAAA=Food and Drug Administration Amendments Act; PREA=Pediatric Research Equality Act.
*Indicates publication in the peer reviewed literature or results reporting on ClinicalTrials.gov.

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Full competing interests details included on bmj.com.
Data requests can be made to the corresponding author.