Routine telephone review of asthma

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Mortality associated with foodborne bacterial gastrointestinal infections

Statistical method is worth examining

Editor—Helms et al report a significant association between common foodborne infectious, including campylobacteriosis, and increased short term and long term mortality. As this conflicts with conventional clinical wisdom, it is worth scrutinising the statistical method supporting the claim.

Helms et al compare ill cases with healthier (general population) controls by using a comorbidity index to adjust for the fact that underlying conditions were more common among patients in the control group, particularly AIDS related illness, metastatic cancers, and lymphomas or leukaemia. But even after adjusting for comorbidity, the relative mortality fell only from 3.10 to 2.56.

Both the small impact of comorbidity adjustment and the association between infections and morbidity can be explained by known limitations of the Charlson comorbidity index. For example, for lung cancer survival, the Charlson index explained only 2.0% of the variation in survival. It has not been validated for gastrointestinal infections in AIDS and leukaemia patients. Thus Helms et al rely on an index that accounts for relatively little of the variance in mortality rates. They attribute the remainder to bacterial pathogens. But underlying illness provides a more plausible explanation.

Severe illness predicts increased mortality, infections, and comorbidity. The comorbidity index does not fully reflect mortality consequences of illness, so residual confounding by illness, even after conditioning on the index, creates a statistical association between infection and mortality, although the former does not cause the latter.

Imperfectly controlled residual confounding can explain counterintuitive statistical associations between exposures and health outcomes. Before accepting that infectious diarrhoea triples death rates, as Helms et al say, it is appropriate to consider more carefully the non-causal association between infection and mortality from incompletely controlled confounding.

Louis Anthony Cox Jr president
Cox Associates, 503 Franklin Street, Denver, CO 80218, USA

Competing interests: LC has conducted research since 1995 on campylobacter causes and risk analyses. This work has been partly supported by funds received from the US Food and Drug Administration and from the Animal Health Institute. This comment reflects the author's opinions only, and has not been supported by any funders.


Case selection and clinical data are important

Editor—The article by Helms et al raises the importance of case selection and clinical data on the estimates of short and long term mortality from clinical illness. Clinicians’ understanding of an illness entails identifying symptoms and signs, in relation to age, sex, and geography, the three variables for which the authors selected controls. But clinicians also decide on the necessity for diagnostic laboratory tests. Results deemed unlikely to influence patients’ management or outcome affect the likelihood of investigation. Variations in laboratory testing protocols and methods affect what is detected and reported.

Medical epidemiologists are aware that the infecting dose affects severity. In general, the larger the infecting dose, the more severe the illness and the more likely the patient is to present to a clinician, so that severe illnesses are more likely to be represented in those studied.

Medical microbiologists are aware, as acknowledged by the authors, that among the several thousand different salmonellas, some, such as Salmonella typhi, S choleraesuis, S dublin, and S paragallinarum seem predisposed to severe illness and bacteraemia. Similar variation in severity occurs with Shigella and Campylobacter.

One way to deal with the estimate of short and long term mortality is to obtain clinical information concerning mortality. Helms et al think that deaths occurring within one year may relate to the bacterial cause of illness. If a review of the death certificates might give an incomplete picture, examining hospital records could reduce the difficulty.

The method used, as suggested by Evans’s commentary, relates to estimates of an exposure that affects mortality, making full use of the extraordinary data available in Denmark and other Scandinavian countries. Incorporating clinical information about cause of death might clarify whether the observations concern clinically severe cases, or represent other factors, not related to the gastrointestinal infection.

Sarah J O’Brien head of gastrointestinal diseases division
Health Protection Agency, Communicable Disease Surveillance Centre, London NW9 SEQ sarah.o.brien@hpa.org.uk

Roger A Feldman emeritus professor of clinical epidemiology
Barts and the London, Queen Mary School of Medicine and Dentistry, University of London E1 2AD

Competing interests: RAF reviewed published and unpublished epidemiological data relating to campylobacter on behalf of Bayer and the US Food and Drug Administration’s centre for veterinary medicine.


Mechanism needs to be explained

Editor—Helms et al show that gastroenteritis due to one of four common bacterial pathogens increases nearly three times the likelihood of death within a year, even after certain comorbidities are controlled for.

There seems intuitively no reason why a clinically self limiting acute gastroenteritis should cause death except (unusually) as an immediate result of the infection. Could the people at greatest risk of these infections have a lifestyle of dependence on fast food and unsatisfactorily cooked or stored food that is associated with greater mortality? Were Helms et al able to compare the lifestyles of their patients and their controls in a way that might show relative social deprivation? Or do the authors think that these
four infections may cause death by some specific mechanism in the subsequent 12 months? If so, can they suggest what it is?

Philip P Mortimer director Sexually Transmitted and Blood Borne Virus Laboratory, Central Public Health Laboratory, London NW5 5HT

Competing interests: None declared.

Authors’ reply

Editor—Our study was unique because it included patients with infectious gastro-enteritis, by and large people who sought care from their family doctor and had no severe underlying illness. The concerns that O’Brien and Feldman raise about bias introduced by case selection is likely to be less relevant in Denmark as the Danish counties reimburse laboratory costs, and for epidemiological reasons doctors often request stool specimens. Our study was the first to determine mortality while adjusting for background mortality. This was pivotal because gastrointestinal infections often affect elderly people. Furthermore, we adjusted for comorbidity by using data from the national discharge registry. We applied the principles described by Charlson et al, but calculated new empirical weights based on the actual survival rates of the large background population. This approach was used to ensure that the weights were valid and appropriate in the given context. This approach takes care of most of the concerns expressed by Cox. We also found excess mortality in the subanalysis, when all individuals with underlying illness had been excluded.

Many acute infections, including foodborne bacterial infections, are associated with short and long term complications. These include acute complications such as severe dehydration, misdiagnosis of abdominal cramps, leading to surgery, or spread of the pathogens into the bloodstream. Salmonellas are a well known cause of focal and vascular infections.1-3 The Guillain-Barré syndrome is a severe reactive complication to a campylobacter infection,4 although each of these events is uncommon, taken together they may account for our findings.

We agree with O’Brien and Feldman that both the infecting dose and subtype of bacterial species are of importance. In the analyses we looked at the effect of specific zoonotic salmonella serotypes. Beyond Salmonella enteritidis, S typhimurium, and S dublin, we could not see any differences, probably because the number of each of the exotic serotypes was too small to see this. Finally, antimicrobial drug resistance may be associated with adverse public health effects.5

The biological plausibility is supported by the fact that our estimates are in line with common knowledge of the different agents. For example, mortality after salmonella infection was higher than after campylobacter infection, and in the group of Salmonella infections, serotype dublin, known to be invasive, was associated with a marked excess mortality. Although long term mortality was observed for Salmonella, Campylobacter and Versinia enterococitica, the proportion of deaths attributable to the infection was highest in the acute phase. The table was prepared based on the figures in our table 2. The relative mortality has been converted to the attributable proportion of deaths among exposed, that is, a measure of the probability of a death being related to the gastrointestinal infection. In our opinion, the patterns presented in the table makes sense from a clinical point of view, and supports the notion that our findings are more than artefacts.

Morten Helms research fellow
Pernille Vastrup statistician
Kåre Mølbak staff specialist
Statens Serum Institut, DK-2500 Copenhagen, Denmark

Competing interests: KM reviewed data relating to Campylobacter on behalf of US Food and Drug Administration’s centre for veterinary medicine for an administrative hearing concerning a proposed withdrawal of the fluoroquinolone enrofloxacin (Baytril, Bayer) for use in poultry. Please note: Dr Feldman and Cox Associates reviewed similar data on behalf of Bayer.


1 Mortality data among 48 857 patients infected with salmonella, campylobacter, shigella, and Versinia enterococitica. Mortality is expressed as the cumulative mortality risk in a time interval after infection and the proportion of these deaths attributable to the gastrointestinal infection

<table>
<thead>
<tr>
<th>Species</th>
<th>Mortality risk per 1000</th>
<th>Attributable proportion (%)</th>
<th>Mortality risk per 1000</th>
<th>Attributable proportion (%)</th>
<th>Mortality risk per 1000</th>
<th>Attributable proportion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>12.3</td>
<td>92</td>
<td>10.8</td>
<td>55</td>
<td>8.1</td>
<td>35</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>2.7</td>
<td>85</td>
<td>5.0</td>
<td>46</td>
<td>4.1</td>
<td>26</td>
</tr>
<tr>
<td>Shigella</td>
<td>3.0</td>
<td>95</td>
<td>—</td>
<td>NS</td>
<td>—</td>
<td>NS</td>
</tr>
<tr>
<td>Versinia</td>
<td>1.7</td>
<td>72</td>
<td>3.5</td>
<td>60</td>
<td>—</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS-no significant excess mortality.

Mortality in Swedish women with cosmetic breast implants

Study found increased risk of suicides and cancer deaths

Editor—The increased suicides and lung cancers among implant patients reported by Koot et al is consistent with a study by Brinton et al at the US National Cancer Institute.1 However, Brinton et al found an increased risk of suicides and cancer deaths compared with other patients having plastic surgery. If plastic surgery patients have more psychological problems than the general population, as Koot suggests, that would not explain the difference between suicide rates of breast augmentation patients compared with other plastic surgery patients. There are other, more likely explanations. Notably, unlike most other plastic surgery patients, implant patients suffer from well documented complications such as chronic pain and implant breakage that increase in likelihood every year. Our centre receives letters every week from women whose implants are broken and who cannot afford explant surgery. Many of these women are quite desperate, especially when silicone is migrating to other organs or causing pain or deformities. Even in countries with national health care, these problems can be difficult to remedy and could potentially cause an increase in suicides.

A flaw of the Koot et al study is that it included women who had breast implants for less than one year, which weakens the statistical power. In contrast, the Brinton et al study included women who had breast implants for at least eight years and found increases in deaths from suicide, lung cancer, and brain cancer compared with plastic surgery patients who reported similar smoking and lifestyle habits.

Diana Zuckerman president
National Center for Policy Research for Women and Families, 1901 Pennsylvania Avenue, NW Suite 901, Washington, DC 20006, 202 223-4000, USA

dz@center4policy.org

Competing interests: None declared.

1 Koot VCM, Peters PHM, Granath F, Goegeb EE, Nyersen O. Total and cause specific mortality among Swedish women with cosmetic breast implants: prospective study. BMJ 2003;326:527-8 (8 March)


Body dysmorphic disorder should be considered

Editor—Koot et al reported an increased risk of suicide among patients who had received cosmetic breast implants.1 The somatoform disorder known as body dysmorphic disorder entails a preoccupation with a defect in appearance, and the defect is either imagined, or, if a slight physical defect is present, the patient’s concern is markedly excessive with subsequent impairment of social or occupational functioning.2 The patient’s distress may lead to suicidal ideation, suicide attempts, and
completed suicide. It has been estimated that between 6% and 15% of patients having cosmetic surgery and dermatology suffer from this disorder. Consequently, cosmetic surgeons should seek psychiatric consultations preoperatively for the purpose of ruling out body dysmorphic disorder and have it treated if present. Perhaps only then can the elevated suicide rate associated with breast implants be diminished.

Jordan Klesmer assistant professor of psychiatry New York University School of Medicine, North Shore University Hospital, 400 Community Drive, Manhasset, New York 11030, USA

klesmer@nshs.edu

Competing interests: None declared.


Routine telephone review of asthma

Measurement of quality dimensions causes concern

Editor—The study by Pinnock et al on routine telephone review of asthma can be considered from the perspective of performance on the dimensions of appropriateness, accessiblity, efficiency, safety, effectiveness, and acceptability. This study indicated that, without clinical disadvantage or loss of satisfaction, telephone consultations provided an efficient option for the routine review of asthma. These findings require further consideration.

The sample does not seem representative of the target population. This is important because the assessment of care is dependent on the group studied. In addition to the authors’ concerns about generalisability, our concerns are that 75% of eligible patients did not participate and recruitment was unequal between groups. As such, appropriateness and effectiveness for the target population cannot validly be determined.

Patients who withdrew may indicate dissatisfaction. Access, acceptability, and effectiveness of care is questionable.

Competing interests: None declared.


Further investigation is required

Editor—Pinnock et al conclude that telephone consultation for asthma review is an efficient option for patients in primary care. We have several concerns about this study. Firstly, a large number of patients (654/932) chose not to take part, and a further 307 were excluded for other reasons. It is not inconceivable that patients who dislike telephone consultations could have entirely opted out even before the study started.

Secondly, the assumption that actual observation of patients’ inhaler technique and peak flow measurement is equivalent to asking patients about their technique or measurements causes concerns. Patients commonly deny problems using inhalers but often fail to demonstrate effective usage.

Thirdly, the conclusion that both interventions were equally effective is somewhat spurious since, using their own instrument, neither intervention produced a difference in outcome three months later. It might be better to say both were equally ineffective.

Lastly we found in our randomised control trial of telephone triage versus face to face consultations for appointments on the same day that one of the main differences between the two types of consultation was the undertaking of opportunistic health promotion. It would have been interesting to know if anything other than asthma management (for example routine blood pressure measurements) was going on in these 20 minute appointments. We believe further investigation of these problems is required before recommending this method of managing asthma.

Brian McKinstry senior researcher Community Health Sciences, Edinburgh University, Edinburgh EH18 9DZ

Dee Hasney senior researcher Highlands and Islands Health Research Institute, University of Aberdeen, Beechwood Business Park North, Inverness IV2 3ED

Jeremy Walker research fellow Research Unit in Health, Behaviour and Change, University of Edinburgh Medical School, Edinburgh EH18 9AG

Sally Wyke director, Scottish School of Primary Care Lister Institute, Edinburgh EH18 9DR

Competing interests: None declared.


Authors’ reply

Editor—We acknowledged in our discussion that only a third of eligible patients participated in our trial raising concerns about generalisability. Having identified a group...
Consumption of coffee during pregnancy

Article raises more questions than it answers

Editor—Wisborg et al’s article raises more issues than it settles. Firstly, coffee contains not only caffeine but a mixture of different ingredients (milk, sugar, stabilisers, flavour, and other alkaloids from coffee beans). Attributing the result of drinking coffee to just one constituent seems illogical. If Wisborg et al want to prove what they contend, they should contrast the group taking eight cups of ordinary coffee to those taking eight cups of decaffeinated coffee.

Secondly, in many parts of the world, tea, chocolate, and cola are consumed on a large scale and in high doses, like traditional Chinese tea in Hong Kong. Yet Hong Kong has one of the lowest perinatal mortality rates in the world. In Japan and China tea is regarded as part of the healthy diet, to be consumed regularly. The same also applies to cola in America and many parts of the world. So what will be the combined effect of coffee, tea, chocolate, and cola should the woman be drinking marginal amounts of coffee (four to seven cups)?

One of the gold standards in establishing causal relations between two factors is to show the dose dependent relation. Wisborg et al’s study showed that, statistically speaking, there is a one off increase in stillbirth after eight or more cups of coffee. To illustrate the dose dependent relation better, the last group should have been subdivided into those taking eight to 11 cups, and those taking 12 cups or more.

Caffeine is used widely to treat migraine. If caffeine leads to stillbirth in the form of coffee, it may carry the same risk for women taking it for their migraine. Should we ban women from taking this seemingly harmless drug lest caffeine leads to stillbirth?

Lastly, I have doubts about the estimates of the number of cups of coffee per day (and hence the dose of caffeine). The size of the cup and the extent to which a cup is filled all affect the actual amount of coffee taken as does the brand. So how accurate can your estimate be?

Ludwig Tsoi
Senior Medical Officer
Accident and Emergency Department, North District Hospital, Hong Kong SAR
doctor@cuhk.edu.hk

Competing interests: LT is a coffee, tea, chocolate, and cola lover.

Authors should adjust for history of drug abuse

Editor—We read with interest the article of Wisborg et al.1 The authors support that high maternal coffee consumption during pregnancy is associated with an increased risk of stillbirth but not with infant death. They mention that women with a high intake of coffee are more likely to be smokers and to have a high intake of alcohol. They correctly adjusted their results for smoking and drinking habits. However, they do not provide any information about drug abuse among these women.

Consumption of eight or more cups of coffee is suggestive of addictive behaviour. The use of illegal drugs such as cocaine is associated with an increased incidence of parallel cigarette and alcohol use.2-3 The adverse effect of maternal use of heroin, cocaine, crack cocaine, and benzodiazepines in pregnancy has been adequately documented.4 The use of cannabis may not be a major prognostic factor regarding the outcome of pregnancy but is an indicator of low socioeconomic status and use of other harmful drugs.5

The authors draw the profile of pregnant women who consume high amounts of coffee. They tend to be older, more often multiparous, more likely to be single, less likely to be students, and they had fewer years of education. Interestingly this description matches with the profile of drug users.6 For the above reasons we believe that the exclusion of the information of drug abuse from the study is a methodological error.

Michael Sindos
Clinical Research Fellow
sindosgy@hotmail.com

Narendra Pals
Clinical Research Fellow
Department of Women’s Health, Whittington Hospital, London N19 SNF

Stavroula Michala
SHIO in obstetrics and gynaecology
Women’s Health Directorate, St Thomas’ Hospital, London SE1 7EH

Competing interests: None declared.


Data do not support claim

Editor—Wisborg et al found an association between maternal coffee consumption and risk of stillbirth, and claim that after adjustment for potential confounding factors the association remained significant.1 However, I am not convinced that the data they present support that claim.

The claim of a significant association seems to be based on the statistical significance for the odds ratio that compares the highest consumption group with the


Authors' reply

Entor—In a prospective study we found that coffee drinking during pregnancy was associated with an increased risk of stillbirth, but not with death in infancy.1 Our results on stillbirth seemed to indicate a threshold effect around four to seven cups per day, but the risk estimate in women with the highest intake of coffee was based on only 11 stillbirths and we therefore had no possibility to explore further the relation between coffee and stillbirth in women drinking eight or more cups of coffee per day. Ludwig claims that a dose dependent association is the gold standard for establishing a causal relation. This is not correct. A monotonic, unidirectional dose-response curve is neither necessary nor sufficient for establishing a causal relation.2

Our result may represent a causal relationship or be due to other factors associated with coffee drinking and stillbirth. Sindos et al are particularly concerned about the possibility of unadjusted confounding, because no information was included about drug abuse. Drug abuse, especially of cocaine, among pregnant women is, fortunately, a minor problem in Denmark and identified drug abusers are not included in our cohort.3 Drug abuse including cocaine is thus of little or no relevance as a confounder in our cohort.

Caffeine is regarded as the key component in studies of the potential effects of coffee. The path to death is usually multifactorial, composed of several component causes. Caffeine may just be one causal component that in some settings together with other causal components leads to death but in other settings one or more of the other component causes are missing, or the time specific distribution of these component causes is different.

As for Jacobs's criticism of our statistical approach we believe that pairwise comparisons between each level of coffee intake and the reference category is technically appropriate, even if other approaches could have been chosen. Coffee is a commonly consumed stimulant and if our results represent a true causal relationship it has important health implications. However, the question on a causal relation is still open. Thus in an ongoing randomised study including 1000 pregnant women we are further exploring the effect of coffee with and without caffeine.

Kirsten Wisborg kwisborg@perinatal.dk
Department of Obstetrics and Gynaecology, Aarhus University Hospital

Competing interests: None declared.

1 Ludwig A. Moderate coffee consumption and stillbirth. BMJ 2003;326:420-2. (22 February)


4 Ludwig A. Relationship between provider and servant is too old fashioned for the modern world. BMJ 2003;326:511-2. (25 March)

5 Macdonald S. Doctors are servants of patients says chief medical officer. BMJ 2003;326:509. (15 March)

6 Macdonald S. Doctors are servants of patients, says chief medical officer. BMJ 2003;326:509. (15 March)

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31 Macdonald S. Doctors are servants of patients, says chief medical officer. BMJ 2003;326:509. (15 March)